A Toxicological Assessment of Five Metals with Implications in Canadian Mining

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A Toxicological Assessment of Five Metals with Implications in Canadian Mining

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PREFACE

Each year,
students in the advanced
undergraduate course, Topics in
Toxicology, TOX-4200, research, write,
edit, and publish a class report. This is done
to enhance their understanding of the
science of toxicology and its use in risk
assessment. This also provides skills in
teamwork and attainment of deadlines.
The subjects of these reports vary but all
address issues in human and
environmental toxicology. Some are
completed as contracts, other at the
suggestion of the students, professors, and
outside experts. This report was prepared
at the suggestion of members of the class of 2008.
The report is the product of the students in
the class and undergoes only minor editing
by the professors teaching the course.

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TABLE OF CONTENTS

INTRODUCTION……vi

1 CADMIUM……1
1.1 Identity……1
1.2 Characteristics……1
1.3 Mammalian Health Assessment……3
1.4 Environmental Fate……9
1.5 Environmental Health Assessment……11
1.6 Conclusions……15
1.7 References……16

2 COBALT……21
2.1 Identity……21
2.2 Characteristics……21
2.3 Mammalian Heath Assessment……22
2.4 Environmental Fate……32
2.5 Environmental Heath Assessment……34
2.6 Conclusions……37
2.7 References……38

3 COPPER……45
3.1 Identity……45
3.2 Characteristics……45
3.3 Mammalian Health Assessment……46
3.4 Environmental Fate……52
3.5 Environmental Health Assessment……54
3.6 Conclusions……58
3.7 References……60

4 NICKEL……67
4.1 Identity……67
4.2 Characteristics……67
4.3 Mammalian Health Assessment……69
4.4 Environmental Fate……92
4.5 Environmental Health Assessment……93
4.6 Conclusions……99
4.7 References……100

5 URANIUM……113
5.1 Identity……113
5.2 Characteristics……113
5.3 Mammalian Health Assessment……114
5.4 Environmental Fate……123
5.5 Environmental Health Assessment……124
5.6 Conclusions……127
5.7 References……128

INTRODUCTION

Canada is among the top producers and exporters of metallic minerals around the world. In 2006, the value of the production of metallic minerals in Canada was estimated to be $21.2 billion, an increase from previous years due to increasing value of these elements (NRC, 2006). As a whole, mining and mineral processing activity made up 3.7% of the 2002 Canadian Gross Domestic Product (GDP) (NRC, 2003), making it a major contributor to the Canadian economy.

The goal of this project was to complete a thorough toxicological assessment of metals relevant to mining in Canada. Cadmium, cobalt, copper, nickel and uranium were selected; each associated with differing mammalian and environmental health issues.

Mammalian Health Assessment

Some metals are essential for the maintenance of good health. They are requirements for synthesis of endogenously produced vitamins, enzyme cofactors and other proteins. Among these, iron is a central constituent to heme, cobalt in an essential component of vitamin B12, and zinc and copper function in a diverse array of enzymes. In some animals, nickel is also thought to have distinct roles. At the same time, metals in excess presents a major health concern. Nickel, cobalt, gold and silver are strong immune sensitizers (induce type IV hypersensitivity reactions), and most metals do have the ability to produce damaging reactive oxygen species.

Environmental Health Assessment

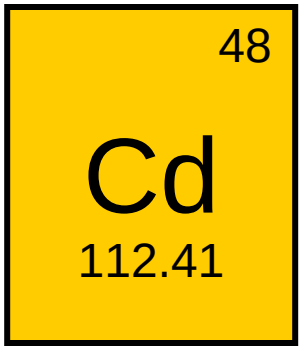
Mining operations are largely considered hazardous to the environment. Today, great effort is placed on employing practices which minimize the negative impact to the ecosystems in which the mines and treatment facilities affect. The proper disposals of mine tailings and acid waste drainage, as well as reducing the physical disruption of the local area are major concerns.

References

Natural Resources Canada (NRC) 2006. Canadian Mining Yearbook.

Natural Resources Canada (NRC). 2003. Mining facts, May 2003.

1 CADMIUM



1.1 IDENTITY

Symbol: Cd

CAS No.: 7440-43-9

Electron configuration: [Kr] $4d^{10}$ $5s^2$

1.2 CHARACTERISTICS

1.2.1 Physical and chemical properties

Table 1-1: Physical and chemical properties of cadmium

Atomic number	48
Atomic mass	112.41
Oxidation states	+1, +2
Stable isotopes	^{106}Cd, ^{108}, ^{110}Cd, ^{111}Cd, ^{112}Cd, ^{113}Cd, ^{114}Cd, ^{116}Cd
Boiling point	1040 K
Melting point	594 K
Density	8.64 g/cm^3
Ionization energies	1st: 867.8 kJ/mol 2nd: 1631.4 kJ/mol 3rd: 3616.0 kJ/mol
Electron affinity	0 kJ/mole
Electronegativity	1.69 (Pauling scale)
Physical description	Soft silver-white metal, hexagonal crystal structure

Reference: ATSDR, 1997

1.2.2 Sources of Cadmium

Cadmium occurs naturally in the Earth's crust, but has no known essential biological function for any plants or animals.

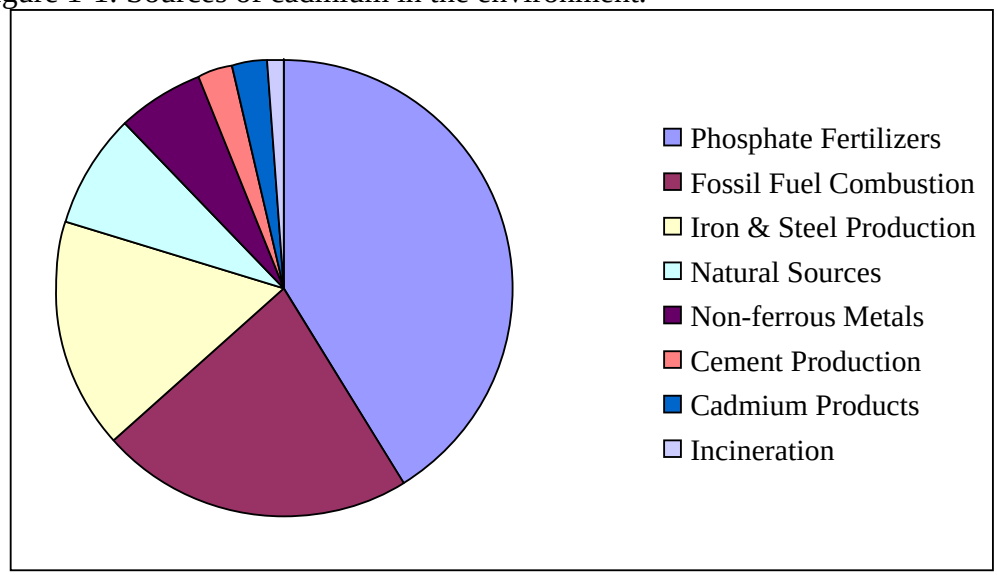
Cadmium is released into the environment through the burning of fossil fuels, the incineration of municipal waste materials, and as emissions from zinc, lead, and copper smelters. Most of the cadmium currently used today is obtained as a byproduct from the smelting of these metals. Cadmium is also used in the manufacture of pigments, batteries,metal-plating, and certain plastics (ATSDR, 1997).

Food is the most significant source of cadmium for most humans, with an exception being cigarette smokers. Rice, durum wheat, sunflower kernels, flax seeds, and shellfish all naturally sequester cadmium from their environments. The extent of exposure through this route for varies with location of agricultural land, which in turn influences soil composition. For example, the application of phosphate fertilizers and sewage

sludge to agricultural fields increases the cadmium content of the soil (ATSDR, 1997), and the burning of coal and refining of ores releases cadmium and may increase cadmium deposit on the plants and soil (Arnold *et al.*, 2006), in turn leading to elevated cadmium levels in plants. An estimated 98% of ingested cadmium comes from terrestrial foods, 1% from aquatic foods, and 1% from drinking water. Collectively, adult daily cadmium intake in from food is 10 - 25 µg; only 0.5 to 1.0 µg of which is actually retained within the body (Arnold *et al.*, 2006).

Cigarette smoke represents a significant source of cadmium to those exposed. It has been shown that smokers have approximately twice as much cadmium retained in their bodies as nonsmokers do, certainly increasing the risk of negative effects (ATSDR, 1997). Exposure routes are illustrated in Figure 1-1 and sources from mining activity in Table 1-2.

Figure 1-1: Sources of cadmium in the environment.



Data taken from: Van Assche, 1998

Table 1-2: Cadmium releases from mines in Canada for 2006

Province	On-site Releases (kg)				Number of Sites*
	Air	Water	Land	Total	
Saskatchewan	9.932	20.2	48.016	78.208	9
Quebec	2451.342	1060.708	103.6	3616.498	80
P.E.I.	0.545	0	0	0.545	1
Ontario	6495.9	1208.336	422.86	8126.732	124
Nova Scotia	15.805	9.202	0	25.007	8
Newfoundland	25.9	23	0	48.1	4
New Brunswick	498.108	447.7	24	970.575	16
Manitoba	29059.9	151.636	0	29211.8	17
British Columbia	299.13	660.6	207	1166.64	53
Alberta	258.178	167.372	203	627.892	46
Canada (total)	39115	3747	1010	43872	358

*industrial sites Reference: NPRI, 2006

1.3 MAMMALIAN HEALTH ASSESSMENT

1.3.1 Toxicokinetics/ toxicodynamics

1.3.1.1 Absorption

The solubility of cadmium has a significant impact on absorptive capability. Only about 5% of ingested cadmium is absorbed, thus the average person retains 0.5 - 1.0 µg of cadmium per d from foodstuff. Higher amounts (25 to 60%) of cadmium are absorbed into the body from air, including inhaled smoke, than ingested from foods. Dermal absorption is considered insignificant (Järup *et al.*, 1998).

Factors influencing absorption of cadmium from food include physiological factors, the chemical form of cadmium present, sex, and the iron and calcium status of the individual. It has been shown that decreased body iron stores increases cadmium absorption to about 10% (from 5%) (IPCS, 1992). Studies have shown that people with low iron have elevated levels of cadmium in their blood (Jarup et al., 1998), and animal experiments have shown that diets low in calcium and protein may be associated with increased intestinal absorption. Preliminary studies have shown that cadmium absorption may be higher in females than in males. The decreased calcium stores in females associated with normal female physiology such as pregnancy are thought to contribute to this (IPCS, 1992).

Pulmonary absorption of cadmium depends on the chemical form, solubility, and particle size of cadmium (IPCS, 1992). Once inhaled, 50-100% of the cadmium will deposit in the alveoli, where it is absorbed. In an adult human, 20-30% of inhaled cadmium is retained in the lung; an estimated 60% of this is absorbed systemically. The amount of cadmium effectively absorbed is less than 0.2 µg per d in the case of chronic exposure. Potential respiratory cadmium can be diverted to the gastrointestinal tract when deposited on the mucosa of the nasopharynx, trachea, or bronchi (IPCS, 1992).

Cigarette smoking adds significantly to cadmium intake. Daily intake of cadmium from smoking one pack of cigarettes per d is an additional 2- 4 µg (IPCS, 1992).

Dermal exposure is an insignificant route of absorption of cadmium and would be of concern only when concentrated solutions are in contact with the skin for several h or longer (ATSDR, 1997).

1.3.1.2 Distribution

The half life of cadmium in the body range from 20- 40 years. The half life is directly related to distribution in the blood and to various target tissues and organs. More than 90% of cadmium is distributed systemically bound to red blood cells or to plasma proteins including serum albumin. The kidney and liver have the highest concentrations of cadmium at steady state, and contain 30% and 20% of the body burden, respectively.

Following acute exposure, cadmium is immediately distributed to the liver via the hepatic portal artery. Cadmium induces the synthesis of metallothionein in the liver and kidney, and shortly after exposure, cadmium redistributes to the kidney as well. Metallothionein-bound cadmium is found in the blood as soon as protein synthesis occurs. This cadmium-metallothionein complex has a low molecular weight, consequently is efficiently filtered through the glomeruli, and reabsorbed by primarily the proximal convoluted tubule (Squibb, 2005). The majority of cadmium remains bound to these metallothionein proteins, and prevents cadmium from exerting toxic effects. Accumulation of cadmium in the human kidney occurs over the entire lifetime (IPCS, 1992).

Cadmium has limited ability for placental transfer from mother to fetus, and depends largely on the developmental stage of the placenta. The cadmium concentration in a newborn human's blood averages 50% lower than in maternal blood (IPCS, 1992).

1.3.1.3 Metabolism

There is no evidence that the divalent cadmium cation undergoes biotransformation in humans.

1.3.1.4 Excretion

In mammals, elimination of absorbed cadmium occurs mainly through the urine. Rate of excretion is proportional to total body burden of cadmium, and is 0.005-0.01% of total body stores. This is equivalent to less that 2 µg/d for most individuals, or up to 3 µg/d for smokers or those occupationally exposed. This value will increase in cases of renal damage.

As such a small percentage of cadmium is absorbed in the gut, the large majority of orally administered cadmium is found in feces.

Cadmium in only excreted in the bile when bound to lipophilic molecules which would normally be excreted through this route.

1.3.1.5 Cellular interactions

Free cadmium is able to bind with to metallothionein with very high affinity, which is protective in that it prevents free cadmium ions from expressing their toxic effects. However upon degradation of metallothionein, free cadmium ions are released and able to enter liver and kidney cells, where they can induce synthesis of additional metallothionein. The metallothionein will then sequester cadmium and protect the cell from the toxicity. However, when the binding capacity of metallothionein is saturated, free cadmium may exist and exert its toxic effects. It has been shown in an *in vivo* study that mice unable to produce metallothionein have greater susceptibility to renal injury and hepatotoxicity (Klaassen, 1999).

Metallothionein is a 6000 Dalton metal- binding protein with 7 sulfhydryl metal-binding sites on each molecule. While zinc generally occupies these sites, cadmium has a greater binding affinity than zinc and is able to displace zinc at each of the binding sites. As mentioned, this protein is inducible by cadmium, and plays a key role in the development of cadmium 'tolerance'. Induction of metallothionein prior to cadmium administration has been shown to decrease some adverse effect of cadmium (Young, 1991). It has also been shown that excess zinc can reduce cadmium toxicity, and conversely, zinc-deficient animals have been shown to be more susceptible to the toxic effects of cadmium (Ercal *et al.*, 2001).

Cadmium may also substitute for selenium, among other metals in metalloenzymes. This renders the enzyme non-functional. It has been shown that humans occupationally exposed to cadmium did have reduced selenium and selenium-dependant enzyme activity (Wasowicz *et al*., 2001).

The high affinity of cadmium for glutathione can produce oxidative injury.
This cadmium-glutathione complex is eliminated in the bile. Additional antioxidant enzymes catalase, manganese-superoxide dismutase, and copper/zinc-superoxide dismutase have been shown to be affected by cadmium (Casalino *et al.,* 2002).

1.3.2 Toxicological data

Table 1-3: Acute toxicity data of cadmium exposure to mammals

Route of exposure	Species	Duration of exposure	Exposure	Response level	Reference
Inhalation	Rat	15 min	46.7 mg/ m^3	LC 50	Barrett *et al.*, 1947
Inhalation	Rat	4 h	229.9 mg/ m^3	LD50	MSDS
Inhalation	Sprague-Dawley rat	2 h	112 mg/ m^3	LC 50	Rusch *et al.*, 1986
Inhalation	Monkey	15 min	940 mg /m^3	LC 50	Barrett *et al.*, 1947
Inhalation	Guinea Pig	15 min	204 mg/ m^3	LC 50	Barrett *et al.*, 1947
Inhalation	Dog	15 min	230 mg/ m^3	LC 50	Barrett *et al.*, 1947
Oral	Rat	N/A	100-300 mg/Kg	LD50	Baer and Benson 1987
Oral	Mouse	N/A	100-300 mg/kg BW	LD50	Baer and Benson 1987
Oral	Mouse	4 h	890 mg/ kg BW	LD50	MSDS

Table 1-4: Chronic toxicity data of cadmium exposure to mammals

Route of exposure	Route of exposure	Duration of exposure (weeks)	Exposure	Response	Response level	Reference
Inhalation	Rat	48	0.030 mg/ m^3	mortality	75%	Baranski and Sitarek, 1987

1.3.3 Toxicity

1.3.3.1 Endocrine toxicity

Cadmium is a known endocrine disrupting compound. It acts on the hypothalamus-pituitary axis and on the pituitary-adrenal axis (Lafuente *et al.*, 2001). The greatest effects of this endocrine disruption are observed in reproductive capabilities.

1.3.3.2 Reproductive and developmental toxicity

Interestingly, Cadmium displays a hormetic effect on reproduction in humans. At very low doses, cadmium stimulates ovarian progesterone production, the hormone responsible for maintenance of pregnancy, and inhibits production at higher doses (Henson and Chedrese, 2004). Female rabbits chronically exposed to cadmium showed increased numbers of disintegrating follicles (Massányi *et al*., 2007).

Cadmium exposure during pregnancy has been shown to affect fetal growth, causing fetal growth restriction (FGR). Low birth weight, premature deliveries and spontaneous abortions have also been observed (Henson *et al*., 2001). It has been suggested that the placenta is the target for cadmium during pregnancy, as abnormalities in placental structure have been observed. One explanation for this effect is the decreased secretion of human chorionic gonadotropin hormone, which is vital during pregnancy (Boadi *et al*., 2001).

In cultured human trophoblast cells, cadmium has been shown to diminish progesterone biosynthesis. As progesterone is essential in maintaining myometrial quiescence, a decrease in synthesis could be the cause of observed premature birth. (Yang et al. 2005)

When exposed to an acute near-lethal oral dose of 60-100 mg/kg BW cadmium, male rats and mice exhibited testicular atrophy and necrosis (Andersen *et al.*, 1988; Bomhard *et al.* 1987; Borzelleca *et al.* 1989), as well as decreased fertility (Kotsonis and Klaassen, 1978). These results were not observed at lower dose acute exposures of 25-50 mg/kg BW (Andersen *et al.* 1988; Bon-hard *et al.* 1987; Dixon *et al.* 1976).

Decreased sperm motility has been observed in male Wistar rats with elevated testicular cadmium levels (Benoff *et al.*, 2008).

1.3.3.3 Immunotoxicity

Cadmium is thought to have a hormetic effect on the immune system. At very low doses, it is thought to be an immunostimulant, and at higher doses it is thought to be immunosuppressive (Marth *et al*., 2000). The immunosupressive effects are particularly detrimental in young children (Schoeters *et al*., 2006).

There have been extensive studies investigating the effect cadmium exposure has on immune responses in animals; however its relevance to humans is not clear. The primary

result of cadmium exposure is a decrease in T-lymphocyte-dependent antibody production, reduced natural killer cell activity and suppressed macrophage activity (Stelzer and Pazdernik, 1983; Cook *et al.,* 1984; Thomas and Imamura, 1986; Blakley and Tomar, 1986). These studies were conducted on young animals with healthy immune systems, and the effects observed in mature animals were markedly reduced (Blakley, 1988).

1.3.3.4 Neurotoxicity

Acute inhalation poisoning may result in restlessness, confusion, and insomnia (Beton *et al.,* 1966; Taylor *et al.,* 1984). Headache has been reported as one of the primary symptoms linked with acute ingestion of cadmium salts. It is unknown how this process takes place, but it is hypothesize that hypoxaemia is responsible for some of the effects (Bernard and Lauwerys, 1986a).

1.3.3.5 Genotoxicity

Cadmium exposure has been linked to a high incidence of chromosomal aberrations (Bauchinger *et al.,* 1976; Deknudt and Leonard, 1975; Deknudt *et al*., 1973).

1.3.3.6 Carcinogenicity

Cadmium has been classified as known human carcinogen by several regulatory agencies including the International Agency for Research on Cancer and the National Toxicology Program. Most notably, epidemiological evidence of workers occupationally exposed to high levels of cadmium in the air have shown increased incidence rates of pulmonary cancer. Risk is correlated with length and concentration of exposure. There has been some epidemiological evidence to suggest an increase in prostate and renal cancer as well. Equivocal evidence exists for cadmium causing cancer in the liver, pancreas and stomach.

1.3.3.7 Cardiovascular toxicity

There are case studies describing hypotension and dysrythmias following acute inhalation of cadmium. Inflammatory changes of the myocardium were also observed in one case (Taylor *et al.,* 1984). Following ingestion of cadmium chloride, there have been reports of hypotension and even shock (Buckler *et al.,* 1986; Bernard and Lauwerys, 1986a).

1.3.3.8 Respiratory toxicity

Initial symptoms following acute poisoning from inhalation include slight irritation of the upper respiratory tract. Within hours, acute pneumonitis may develop as well as chest pain, coughing and dyspnoea. In cases of severe exposure, fulminant pulmonary oedema may develop (Beton *et al.,* 1966; Townshend, 1968; Taylor *et al.,* 1984; Barnhart and Rosenstock, 1984; Yates and Goldman, 1990).

Chronic occupational exposure to cadmium dust and fumes may also result in respiratory effects. Symptoms include mild obstructive lung disease, such as dyspnoea, reduced vital capacity and increased residual volume. In the case of excessive exposure, there may be cases of fibrosis with alveolar damage and emphysema (Lauwerys *et al.,* 1974; Stanescu *et al.,* 1977; Edling *et al.,* 1986).

1.3.3.8 Gastrointestinal toxicity

Following acute ingestion of cadmium compounds, gastrointestinal symptoms are the first to emerge. These may include nausea, vomiting, salivation, diarrhea, and abdominal pain and discomfort (Buckler *et al.,* 1986; Bernard & Lauwerys, 1986a). Inhalation of cadmium containing dust and fumes may also produce a metallic taste, nausea and vomiting, diarrhea and abdominal pain. (Beton *et al.,* 1966; Taylor *et al.,* 1984).

1.3.4 Human risk assessment

The largest exposure risk for the general public comes from cadmium found in cigarettes. While the average person absorbs 1-3 µg of the cadmium from food, one cigarette contains 1-2 µg, 40-60% of which may pass to the lungs. This presents a much larger human health concern.

Air levels of cadmium in U.S. cities are low, ranging from less than 1 ng to 40 ng/m^3. Air levels greater than 40 ng/m^3 may occur in urban areas with high levels of air pollution. Most drinking water supplies contain cadmium at less than 1 µg/L, well below the drinking water standard of 50 µg/L. However cadmium levels in drinking water do vary greatly depending on many factors.

The average level of cadmium in unpolluted soil is about 250 µg/kg. At hazardous waste sites, cadmium levels have been measured in soil at about 4 mg/kg, or 6 mg/L in water.

People living near hazardous waste sites or factories might be exposed to cadmium in the air, through contaminated food, dust or water from accidental releases. Workers may be exposed to cadmium in the air from smelting and refining metals, as well as in plants that make cadmium products such as batteries.

Many steps have been taken to protect people from unnecessary cadmium exposure. The EPA limits the cadmium content of drinking water to 5 µg/L, as well as how much cadmium may be deposited in lakes, rivers, dumps and cropland. Cadmium is not permitted in pesticides. The FDA restrictions cadmium in food coloring to 15 mg/L.

Because cadmium accumulates, the greatest concern is for long term exposure to elevated levels in the diet. The minimal risk level (MRL) for chronic oral exposure (365 d or more) to cadmium is 0.0002 mg/kg/d . There have been no such MRL developed for exposure through inhalation.

The World Health Organization (WHO) has established a daily tolerable intake level of 70 µg of cadmium for an average 70 kg man, and 60 µg of cadmium for the average 60 kg woman. The average daily cadmium intake for people in developed countries has been on the decline from 1970 to 1992 (Van Assche and Ciarletta, 1992). This decrease is likely due to decreases in direct atmospheric deposition of cadmium onto crops and soils.

1.3.5 Treatments and Remediation

With acute cadmium poisoning, it has been suggested that treatment with EDTA may be a useful antidote. There is no treatment for chronic exposure.

1.4 ENVIRONMENTAL FATE

Cadmium is present in nature in the form of complexes with other elements: cadmium oxide (most common), cadmium sulfite, and cadmium chloride. Releases of cadmium into the environment come from a variety of sources: smelting of metal sulfide ores, combustion of fossil fuels, incineration of solid waste, and distributions of biosolids. (Pichtel, 2007)

1.4.1 Air

Cadmium is not known to volatize or form volatile compounds in an aquatic media. It is commonly released into the air on particulates as a byproduct of industrial processes, such as the refinement of other metals like nickel and zinc.

The expected lifetime of cadmium particles in the air post-release is about 5-15 d, depending on climate and atmospheric conditions. As with other particles suspended in air, cadmium particulates are vulnerable to dry deposition and deposition as a result of precipitation (Dobson, 1992).

1.4.2 Soil

Cadmium has not historically been freely available in soils because of the nature of its primary origins bound in mineral deposits. However, recently anthropomorphic additions of cadmium to soils have occurred as a result of the settling of particulates from fossil fuel combustion, soil enrichment through fertilizer application (of which cadmium is a trace contaminant), and the application of sewage sludge, which is relatively high in cadmium to agricultural crops.

The fate of cadmium in soil is largely dependant on the pH of its environment and the complex that it is present in.

Table 1-5: Solid-water partitioning coefficient (K_d) values of ionic cadmium

K_d [m^3/kg]	**pH**
3.0-4.5	1.14x10^-2
5.0	4.52x10^-2

K_d [m^3/kg]	pH
5.5-7.5	0.179
8.0	0.377
8.5-9.5	0.794

Reference: US EPA (1999)

Cadmium is adsorbed into the soil at a greater rate when the soil is alkaline; specifically into silicon and aluminum oxides. As the pH drops below 6-7, cadmium partitions into the soil water as described above. Cadmium has far less affinity for many standard metal adsorbents than copper, zinc, and lead and therefore may be more mobile in the soil under a given condition than these metals. Cadmium is most mobile in soils at pH values at or below 5.0 (because most Cd^{2+} and its complexes have desorbed from soil complexes, Pichtel, 2007).

Cadmium in the soil solution quickly forms outer-sphere complexes with soil colloids; Cd^{2+} forms dipole-dipole bonds with negatively charged regions of other molecules (typically the oxygen in water). This allows the cadmium ion to satisfy its net charge and makes for an easy exchange with negatively charged soil matrix surfaces (Brady and Weil, 2004).

1.4.3 Water

Prevalence and availability of cadmium (as with most other metals) in water depends on total water hardness, total oxidation-reduction potential, and pH.

At pH values less than 8.0, most of the cadmium present is soluble in solution as the Cd^{2+} ion, however cadmium may also form complex ions such as $CdCl^{+}$, $CdHCO_3^{+}$, $CdCl_4^{2-}$, $Cd(OH)_3^{-}$, $Cd(OH)_4^{2-}$ and organic chelates, though normally at lesser levels than the ion alone. At alkaline pH (higher than 8.0), Cd^{2+} precipitates as $Cd(OH)_2$ and the insoluble $CdCO_3$. Once cadmium associates with carbonate, it is less likely to be remobilized in suspension. These reaction complexes are all pH dependent and so when pH changes, so will the proportions of cadmium in various complexed forms. (Manahan, 2000)

Total oxidation-reduction potential in water depends in part on how aerated the media is. In waters with industrial inputs during periods of time where the aquatic environment is anaerobic, the water may contain low soluble concentrations of cadmium, microbial reduction of cadmium binds free sulfate, then forms cadmium bound sulfide which precipitates out of solution. (Manahan, 2000)

Rivers contaminated with cadmium can leach cadmium to surrounding land, either through agricultural irrigation, by dumping of dredged sediments, or through flooding (Forstner, 1980; Sangster *et al.*, 1984).

1.5 ENVIRONMENTAL HEALTH ASSESSMENT

1.5.1 Toxicological data

1.5.1.1 Aquatic organisms

Cadmium is not an essential nutrient for any aquatic organisms, but it can be used by marine diatoms under certain conditions (Eisler, 1985). Under levels of low zinc, some marine diatoms are able to function using an isoform of carbonic anhydrase, which uses cadmium in place of zinc (Lane and Morel, 2000). This role for cadmium is rare, and not required for biological function in any aquatic organisms (Eisler, 1985). Cadmium is toxic to many aquatic species at relatively low concentrations, and a variety of sublethal effects are caused by cadmium intoxication, including decreased growth, reproductive inhibition, and shortened life span (Eisler, 1985). Ambient cadmium concentrations of 10 μg/L and lower can cause decreased growth rates in both freshwater and marine varieties of algae (Eisler, 1985). Freshwater arthropods have exhibited reduced reproduction when exposed to a cadmium concentration as low as 0.7 μg/L, and immobilization when exposed to a cadmium concentration as low as 2.6 μg/L (Eisler, 1985). In marine arthropods, cadmium can cause reduced respiration and molt inhibition (Eisler, 1985). Cadmium exposure causes an array of different effects in fish. Cadmium exposures as low as 2 μg/L can cause disrupted lactic dehydrogenase activity and reduced growth in some fish (Eisler, 1985). These effects are more pronounced under conditions of low salinity and higher temperatures (EPA, 2001). This may explain why freshwater species are, in general, more sensitive to the effects of cadmium than marine organisms.

The ECOTOX database (USEPA, 2008) was used to obtain 96-h LC50s for use in comparing species sensitivity to cadmium exposure. In general, the most sensitive freshwater species are Rainbow trout (*Oncorhynchus mykiss*) with a 96-h LC50 of 4.7 μg/L. Among marine organisms, many crustaceans exhibited the high sensitivities to cadmium exposure, the most sensitive being mud crabs (*Rhithropanopeus harrisii*) with an LC50 of only 0.2 μg/L. The complete 96-h LC50 data can be seen in Table 1-6. Cadmium is often eliminated from organisms slowly and tends to bioaccumulate in some (EPA, 2001). Most fish are generally poor bioaccumulators of cadmium taking approximately 1 month to reach steady state levels of cadmium in their tissues (EPA, 2001). Marine mollusks are quite effective accumulators of cadmium. An examination of some bivalve mollusk revealed a range of 113 to 2150 for bioconcentration factors. It was found that many marine mollusks do not reach a steady state concentration of cadmium in their tissues (EPA, 2001), which may be of concern to the seafood industry. Marine crustaceans are much less effective bioaccumulators of cadmium, with common saltwater crustacean BCFs ranging from 22 to 307 (EPA, 2001).

Table 1-6: Acute toxicity values for cadmium in aquatic species

Species	Common Name	96-h LC50 (μg/L)
Crustaceans		
Rhithropanopeus harrisii	Mud crab	0.2
Palaemonetes pugio	Daggerblade grass shrimp	1.1

Species	Common Name	96-h LC50 (µg/L)
Gammarus pulex	Scud	25
Penaeus chinensis	Fleshy prawn	33
Americamysis bahia	Opossum shrimp	35
Gammarus lacustris	Scud	40
Daphnia lumholzi	Water flea	83
Acartia tonsa	Calanoid copepod	171
Amphiascus tenuiremis	Harpacticoid copepod	224
Asellus aquaticus	Aquatic sowbug	448
Crangon crangon	Common shrimp, sand shrimp	460
Cypris subglobosa	Ostracod	687
Rhepoxynius abronius	Amphipod	1225
Ampelisca abdita	Amphipod	1320
Grandidierella japonica	Scud	3140
Palaemon serratus	Pink shrimp, common prawn	4000
Fish		
Oncorhynchus tshawytscha	Chinook salmon	1.4
Oncorhynchus mykiss	Rainbow trout, Donaldson trout	4.7
Pimephales promelas	Fathead minnow	14
Oryzias latipes	Medaka, high-eyes	16
Morone saxatilis	Striped bass	19
Notemigonus crysoleucas	Golden shiner	3150
Garra mullya	Fish	5400
Lutjanus argentimaculatus	Red snapper	6300
Cyprinus carpio	Common carp	6485
Liza vaigiensis	Square tail mullet	6525
Pagrus major	Red Sea Bream	9179
Mugil cephalus	Striped mullet	13530
Acanthopagrus schlegeli	Porgy	16200
Channa punctata	Snake-head catfish	18500
Lepomis macrochirus	Bluegill	21100
Lagodon rhomboides	Pinfish	23333
Priopidichthys sp.	Plain-head perchlet	23700
Platichthys flesus	Starry, European flounder	24400
Chasmichthys dolichognathus	Agohaze, goby	24617
Girella punctata	Green fish	25250
Insects		
Baetis rhodani	Mayfly	60
Lophopodella carteri	Bryozoa	150

Species	Common Name	96-h LC50 (µg/L)
Chironomus tentans	Midge	656
Pectinatella magnifica	Bryozoa	895
Hexagenia rigida	Mayfly	6200
Ephemerella ignita	Mayfly	12500
Leuctra inermis	Stonefly	29000
Chironomus plumosus	Midge	32000
Chironomus riparius	Midge	103672
Hydropsyche angustipennis	Caddisfly	360000
Mollusks		
Physa fontinalis	Bladder snail	80
Crassostrea rhizophorae	Mangrove oyster	5000
Lamellidens marginalis	Mussel	10000
Mytilus edulis	Common bay mussel, blue mussel	20000
Worms		
Dugesia tigrina	Turbellarian, flatworm	2250
Limnodrilus hoffmeisteri	Tubificid worm, Oligochaete	2650
Dendrocoelum lacteum	Turbellarian, planarian	23220
Polycelis tenuis	Turbellarian	77000
Algae		
Tetraselmis gracilis	Green flagellate	1800

1.5.1.2 Terrestrial organisms

Cadmium is not a biologically essential nutrient for terrestrial organisms. Some of the toxic effects of cadmium have been attributed to cadmium's ability to interfere with the uptake, transport, and use of multiple elements including calcium and potassium (Das *et al.*, 1997). Cadmium toxicity in plants usually manifests itself as stunted growth and/or chlorosis (Das *et al.*, 1997). These symptoms are caused by a variety of factors including inhibition of cell proliferation and certain enzymes, as well as cause genetic damage (Das *et al.*, 1997). This genetic damage has also been shown to occur in animals (Das *et al.*, 1997). The chlorosis seen in plants has been associated with an interaction with foliar Fe (Das *et al.*, 1997). Cadmium has also been shown to interfere with zinc-dependant processes in both plants and animals (Das *et al.*, 1997). Zinc and cadmium share many common properties and cadmium alters the biological function of zinc by competing for binding sites (Das *et al.*, 1997). Some plant species are able to develop a tolerance to cadmium after prolonged exposure, via metabolic changes in these plants to cope with cadmium stress (Das *et al.*, 1997). There are also different concentrations of cadmium throughout the plant, as it accumulates the cadmium in more tolerant areas in order to protect the sensitive areas such as the shoots of the plant (Das *et al.*, 1997). Other plants have the ability to bind metals such as cadmium and sequester it in the roots to protect the rest of the plant (Das *et al.*, 1997). It has also been reported that increased soil pH is

associated with a decreased uptake of cadmium by plants (Das *et al.*, 1997). There is very little mortality data concerning terrestrial organisms and so lethal and non-lethal endpoints have been included, and have been summarized in Table 1-7.

Table 1-7: Toxicity data for terrestrial organisms exposed to cadmium

Species	Common Name	Endpoint	Value	Exposure Duration	Response	Number of Data points	Source
Invertebrates							
Colpoda inflata	Soil ciliate	EC50	0.06 mg/L	24 h	Population growth rate	6	ECOTOX
Orchesella cincta	Springtail	NOEC	40 nmol/g	61 d	Reduction in organism weight	1	ECOTOX
Plectus acuminatus	Soil Nematode	EC50	321 mg/kg	21 d	Reduction in organism weight	1	Kamm-enga *et al.* 1996
Aporrec-todea caliginosa	Earth-worm	LC50	540 mg/kg	56 d	Mortality	1	Khalil *et al.* 1996
Caenorha-ditis elegans	Soil Nematode	LC50	584 mg/kg	24 h	Mortality	4	Donkin and Dusen-bery, 1994
Eisenia fetida	Earth-worm	LC50	911 mg/kg	14-21 d	Mortality	5	Lock and Janssen, 2001
Folsomia candida	Springtail	LC50	1138 mg/kg	14-21 d	Mortality	5	Lock & Janssen, 2001
Eisenia fetida	Earthworm	NOEC	18000 mg/kg	56 d	Whole organism weight	2	ECOTOX
Animal Species							
Coturnix japonica	Japanese Quail	LOEL	75 mg/kg	28 d	Reduction in whole organism, testes and organ weight	7	ECOTOX
Plant Species							
Glycine max	Soybean	LOEL	6 mg/kg	NA	Reduction in Biomass	1	ECOTOX
Spinacia oleracea	Spinach	EC50	10 mg/kg	45 d	Reduction in Biomass and root length	1	Adhikari *et al.*, 2007
Cicer arietinum	Chickpea	EC70	23 mg/kg soil	15 d	Reduction in nodule growth	1	Wani *et al.*, 2007
Sinapis alba	White Mustard	EC50	43 mg/kg	3 d	Reduction in root length	1	ECOTOX
Triticum aestivum	Wheat	EC50	449 mg/kg	3 d	Reduction in root length	1	Caoa *et al.*, 2007

EC- effective concentration; LOEL – lowest observed effect level; NOEC – no observed effect concentration

1.5.2 Risk Assessment

Due to the relatively low phytotoxicity, its tendency to bioaccumulate, endocrine disrupting effects, and mobility in the soil (where present), cadmium may pose significant risk to animals (including humans) who are chronically exposed via the plants they eat. Cadmium at relatively low concentrations (1 µg/g) was shown to hinder gonadal development in freshwater turtle (*Trachemys scripta* and *Chrysemys picta*) embryos (Callard and Kitana, 2008). Endocrine disrupting effects have also been observed in rats, clams, mollusks, crustaceans and fathead minnows all at levels representative of possible exposures at contaminated sites, 25-40 µg/L (Zhang and Jia, 2007; Damak et. al, 2007; Ketata et al, 2007; Rodríguez, 2007; Sellin, 2006).

Natural environmental cycling occurs minimally with cadmium; however with the recent the increase in the applications of sewage sludge to agricultural crops, exposure cycles have developed. Typically, crops take up cadmium from the soil and retain it, humans and animals then may ingest the cadmium-containing plants. Human and animal waste can be distributed over future crops as fertilizer. In this way cadmium is recycled back into the soil.

1.5.3 Treatments and Remediation

As with other metals whose mobility is limited in aquatic and terrestrial systems by the pH of the media, most treatment and remediation is performed by the addition of lime to the system. This addition increases the pH and thus shifts the K_d value, and availability in that soil organisms. Due to the ability of some plants to hyper-accumulate cadmium with little to no ill effects phytoremediation is possible. Such plants could then be removed from the system and disposed of in a proper way.

1.6 CONCLUSIONS

Cadmium is a metal released into the air by combustion of fossil fuels and the smelting of zinc, lead, and copper. Exposure for the average person is through food consumption of cadmium accumulating plants. Due to high cadmium levels present in tobacco plants, smoking greatly increases exposure to cadmium, as does occupations that involve exposure to cadmium fumes or cadmium-containing compounds. The World Health Organization (WHO) has established a daily tolerable intake level of 70 µg of cadmium for an average 70 kg man, and 60 µg of cadmium per d , for the average 60 kg woman.

The way in which cadmium is absorbed and utilized means that people with low levels of iron and zinc will be more susceptible to cadmium toxicity, as well as women, who absorb cadmium more readily than males. Due to the tendency of cadmium to bioaccumulate, as well as its significantly long 20-40 year half life, it is possible that it may pose a risk to animals, including humans, in long-term chronic exposure situations.

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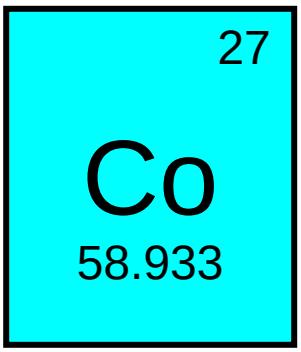
2 COBALT



2.1 IDENTITY

Symbol: Co

CAS No.: 7440-48-4

Electron configuration: [Ar] $4s^2$ $3d^7$

2.2 CHARACTERISTICS

2.2.1 Physical and chemical properties

Table 2-1: Physical and chemical properties of cobalt.

Atomic number	27
Atomic mass	58.93320 g/mol
Oxidation states	0, +2, and +3
Stable isotopes	^{59}Co
Radioactive isotopes	There are 26 radioactive isotopes, including: ^{56}Co, ^{57}Co, ^{58}Co, ^{60}Co
Boiling point	3337 K
Melting point	1766 K
Density	8.90 g/cm^3
Ionization energies	1st: 760.4 kJ/mol 2nd: 1648 kJ/mol 3rd: 3232 kJ/mol 4th: 4950 kJ/mol
Electron affinity	63.7 kJ/mol
Electronegativity	1.88 (Pauling scale)
Physical description	Silvery gray solid at room temperature

Reference: ATSDR 2004

2.2.2 Sources

Cobalt is the 33rd most abundant element on Earth, and amounts to approximately 0.0025% of the weight of Earth (Kim *et al.* 2006). It commonly is present in nature complexed as sulfides, arsenides, or oxides (Barceloux 1999). The most common forms include $CoAs_{2-3}$ (smeltite), CoAsS (cobaltine), and Co_3S_4 (linneite) (Kim *et al.* 2006).

Small amounts of cobalt are present naturally in rocks, soil, water, plants, animals (ATSDR 2004) and volcanoes (Kim *et al.* 2006). It may enter the air after erosion and weathering of rocks and soil, spray of seawater, forest fires, plant extractions, and continental and marine biogenic emissions (Kim *et al.* 2006). It also occurs naturally in seawater, surface water, spring water, and groundwater (Kim *et al.* 2006) in a dissolved/ ionic form (ATSDR 2004). Surface water may acquire cobalt through runoff and leaching of nearby soil and rock (ATSDR 2004).

Humans are exposed to cobalt through many anthropogenic sources including the mining and processing of cobalt-containing ores, use of cobalt-containing sludge, presence of phosphate fertilizers in soil, the disposal of cobalt-containing waste, atmospheric deposition from burning of fossil fuels, the refining of metals (Kim *et al.* 2006), and from vehicle exhaust (ATSDR 2004). The ores usually associated with cobalt are copper, nickel, silver, lead, and iron (ATSDR 2004). Approximately 44% of cobalt comes from nickel ores (Kim *et al.* 2006). As well, through polishing of diamonds with cobalt containing disks, a cobalt powder can be released to the air (Lauwerys and Lison 1994). In typical industries including hard metal manufacturing, welding, grinding, or from the sources listed above, workers are exposed by inhalation of cobalt dust, where air concentration of cobalt ranges from 0.01-1.7 mg Co/m^3 (ATSDR 2004).

The major source of human exposure to cobalt through the ingestion of foods containing cyanocobalamin (vitamin B12). Cobalt is a central component to vitamin B12, making cobalt an essential nutrient (Barceloux 1999). High levels also occur in fish and vegetables (Barceloux 1999). Small amounts are present in drinking water, ranging from 0.1-5 .0 µg Co/L (Barceloux 1999). In Canada, the average intake of inorganic cobalt from the diet is 11 µg/d (Kim *et al.* 2006).

Table 2-2: Cobalt releases from mines by province

Province	**On-site Releases (tonnes)**				**Number of Sites***
	Air	Water	Land	Total	
Saskatchewan	0	0	0	0.002	3
Quebec	0	0	0	0	6
Ontario	4.103	0.283	0	4.505	35
Nunavut	0	0	0	0	1
Nova Scotia	0.009	0	0	0.009	3
Newfoundland	0.223	0	0	0.223	1
New Brunswick	0.1	0	0	0.1	1
Manitoba	5.3	0.397	0	5.7	1
British Columbia	0.004	0	0	0.005	5
Alberta	0.621	0	0	0.713	11
Canada (total)	10	0.680	0	11	68

*industrial sites

Reference: NPRI, 2006

2.3 MAMMALIAN HEALTH ASSESSMENT

2.3.1 Toxicokinetics/ toxicodynamics

2.3.1.1 Absorption

Inhalation is a major exposure route to cobalt. Inhaled cobalt can be absorbed through two mechanisms, depending on the size of the particles inhaled. Larger particles, greater than 2 µm in diameter, will deposit in the upper respiratory tract, where high airstream velocities and airway geometry encourage inertial impaction of the particles (Kim *et al.* 2006). In upper portions of the tract, they can transfer to the gastrointestinal tract through

mucociliary and swallowing action. These mechanical clearance mechanisms outweigh tendency to travel farther down the respiratory tract, particularly with larger particles. Smaller particles may deposit in the lower respiratory tract, where there are lower airstream velocities and a different airway geometry which allow particles to avoid inertial impaction (ATSDR 2004). Particles reaching the lower respiratory tract undergo the process of sedimentation, diffusion (Kim *et al.,* 2006), and electrostatic precipitation (ATSDR 2004). Cobalt particles in the lower respiratory tract will be phagocytozed by macrophages (ATSDR 2004). In humans, particles with a diameter ranging from 0.8 to 1.7 μm are five times more likely to reach the lower respiratory tract than undergo mechanical clearance (Kim *et al.* 2006).

Cobalt present in foodstuff is absorbed orally. In humans, bioavailability varies between 18% and 97% depending on factors such as quantity, type of cobalt compound, and nutritional status of the individual (ATSDR 2004). For example, iron deficiency has been shown to be a nutritional factor capable of increasing the absorption of cobalt in both humans and rats (ATSDR 2004).

Cobalt may be absorbable through the skin. Dermal contact with cobalt-containing dust has been shown to result in an increase in urinary cobalt levels, and lead to the incorporation of cobalt in fingernails. In guinea pigs, it has been shown that the absorption of cobalt is 80% in abraded skin; while very low less than 1% in intact skin (ATSDR 2004).

2.3.1.2 Distribution

The highest levels of cobalt in the human body are found in the liver, followed by the kidney (Barceloux 1999). Since it is an essential component of vitamin B12, it is also found in many other tissues including muscle, lung, lymph nodes, heart, skin, bone, hair, stomach, brain, pancreas, plasma, and urinary bladder (ATSDR 2004). The total body burden of cobalt is approximately 1.1-1.5 mg in humans, about 0.11 mg of which sequestered in the liver (Kim *et al.* 2006). Cobalt does not accumulate within the body as aging occurs (Barceloux 1999).

Cobalt was found to distribute in larger amounts to the lymph nodes, liver, spleen, and kidneys in metal workers exposed to cobalt in the air. Metal workers, and individuals employed near coal mines and copper smelters have been found to accumulate significantly higher amounts of cobalt in the lungs than compared to control populations (Kim *et al.* 2006). Experimental animals exposed to cobalt in the air also had high levels of cobalt in the lungs. Histological samples from these animals showed that the cobalt particles concentrated within macrophages of the bronchial wall or interstitium near the terminal bronchioles. In these animals, cobalt mainly distributed to the liver and kidney, with significant concentrations in the trachea, spleen, bones, and heart (ATSDR 2004).

In pregnant rats, oral exposure caused cobalt to accumulate in the fetal blood and amniotic fluid. Long term oral exposure of cobalt chloride in rats showed significantly elevated levels of cobalt in the liver, kidney, muscle, brain, and testes (Kim *et al.* 2006).

A case study on two humans showed that, after intravenous injection of cobalt chloride, distribution was highest in the liver and bladder (Kim *et al.* 2006). Rats exposed intravenously to cobalt chloride showed similar results, with 22.8% accumulation in liver, 10.2% in kidneys, and 3.2% in the intestines (ATSDR 2004).

2.3.1.3 Metabolism

No data concerning the metabolism of cobalt were available.

2.3.1.4 Excretion

Insoluble cobalt compounds seem to follow three-phase kinetics (ATSDR 2004). Mucociliary clearance is the first of the phases which eliminates particles that are deposited in the tracheobronchial region. This process has a half-life of 2 - 44 h. The second phase is macrophage-mediated clearance of particles within the lungs. The half-life of this phase is 10 - 78 d. The third phase, with a half-time in the range of a couple years, corresponds with a long-term lung clearance (ATSDR 2004).

Following inhalation exposure in humans, urinary excretion of cobalt gradually increases as time passes (Kim *et al.* 2006). Approximately 80-90% of absorbed cobalt will have a half-life of several d upon inhalation (Barceloux, 1999). Size of cobalt particles is another factor regarding rate of excretion as larger particles are more susceptible to mechanical clearance to the gastrointestinal tract. The solubility greatly affects the rate of excretion within animals. Soluble cobalt (II) oxide is cleared from the lungs at a faster rate than the less soluble form, cobalt (II, III) oxide (Kim *et al.* 2006).

Fecal elimination is the primary route of excretion for both humans and other animals that are exposed to cobalt orally. There is a large range in excretion rates (3-99%) due to many factors including the quantity of cobalt, the form of cobalt, and the nutritional status of the subject. In both humans and animals, iron deficiency resulted in decreased fecal elimination (ATSDR 2004). Fecal clearance was shown in animals to be largely dependent on the solubility of the cobalt particles, an increase in soluble particles will decrease fecal clearance and a decrease in soluble particles will, in turn, increase fecal elimination (Kim *et al.* 2006).

In an *in vivo* hamster study, cobalt chloride was shown to be excreted through the urine within 48 h of dermal exposure (Kim *et al.* 2006).

2.3.1.5 Cellular interactions

Cobalt is an essential element to humans, required as a component of vitamin B12 (cyanocobalamin)(ATSDR 2004). Cobalt associates with the molecule through unique cobalt-carbon bonds. As part of vitamin B12, cobalt helps acts as a cofactor in numerous enzymatic reactions including those necessary for cell synthesis, nerve maintenance, and reforming the folate coenzyme (ATSDR 2004).

2.3.2 Toxicological data

2.3.2.1 Acute toxicity

Table 2-3: Acute toxicity values of cobalt and related compounds.

Route of Exposure	Compound	Species	Duration of Exposure	Dose	Response	Response Level	Reference
Inhalation	Cobalt sulfate	Mouse	16 d	0.2 mg/m^3	Respiratory	NOAEL	NTP (1991)
Inhalation	Cobalt sulfate	Mouse	16 d	1.9 mg/m^3	Respiratory tract inflammation	LOAEL	NTP (1991)
Inhalation	Cobalt	Rat (SD-Jcl)	4 d	2.12 mg/m^3	Damaged respiratory tissue	LOAEL	Kyono *et al*, (1992)
Inhalation	Cobalt	Rat (SD-Jcl)	5 h	2.72 mg/m^3	Respiratory	NOAEL	Kyono *et al*, (1992)
Inhalation	Cobalt Hydro-carbonyl	Rat	30 min	7 mg/m^3	Respiratory	NOAEL	Palmes *et al*, (1959)
Inhalation	Cobalt sulfate	Rat	16 d	19 mg/m^3	Necrosis of thymus	LOAEL	NTP (1991)
Inhalation	Cobalt sulfate	Rat	16 d	19 mg/m^3	Testes atrophy	LOAEL	NTP (1991)
Inhalation	Cobalt sulfate	Mouse	16 d	19 mg/m^3	Respiratory tract necrosis	LOAEL	NTP (1991)
Inhalation	Cobalt sulfate	Mouse	16 d	19 mg/m^3	Hepatic necrosis	LOAEL	NTP (1991)
Inhalation	Cobalt hydro-carbonyl	Rat	30 min	26 mg/m^3	Edema	LOAEL	Palmes *et al*, (1959)
Inhalation	Cobalt Hydro-carbonyl	Rat	30 min	83 mg/m^3	Severe edema	LOAEL	Palmes *et al*, (1959)
Oral	Cobalt nitrate	Rat (Wistar)	30 d	6.4 mg/ kg BW/d	Alteration in cholinergic sensitivity	LOAEL	Vassilev *et al.* 1993
Oral	Cobalt chloride	Rat CFY	21 d	12.4 mg/kg BW/ d	Decreased body weight	LOAEL	Morvai *et al.* 1993
Oral	Cobalt chloride	Rat CFY	21 d	12.4 mg/kg BW/ d	Multifocal myocytolysis	LOAEL	Morvai *et al.* 1993
Oral	Cobalt chloride	Rat Long-Evans (Female)	3 d	20 mg/kg BW/ d	Body weight	NOAEL	Wellman *et al.* 1984
Oral	Cobalt chloride	Rat (Wistar)	1 d	42.4 mg/kg BW/d	Mortality	LD50	Singh and Junnarkar 1991
Oral	Cobalt fluoride	Rat (Wistar)	1 d	42.6 mg /kg BW/d	Swollen proximal tubules	LOAEL	Speijers *et al.* 1982
Oral	Cobalt fluoride	Rat (Wistar)	1 d	42.6 mg/ kg BW/d	Hepatic	NOAEL	Speijers *et al.* 1982

Route of Exposure	Compound	Species	Duration of Exposure	Dose	Response	Response Level	Reference
Oral	Cobalt fluoride	Rat (Wistar)	1 d	68.2 mg/ kg BW/d	Hyperemia	LOAEL	Speijers *et al.* 1982
Oral	Cobalt chloride	Mouse Swiss-Webster	2 d	76.4 mg/kg BW/d	Alteration of serum proteins	LOAEL	Bryan and Bright 1973
Oral	Cobalt chloride	Mouse Swiss-Webster	1 d	89.3 mg/kg BW /d	Mortality	LD50	Singh and Junnarkar 1991
Oral	Cobalt fluoride	Rat (Wistar)	1 d	91 mg/kg BW/ d	Mortality	LD50	Speijers *et al.* 1982
Oral	Cobalt chloride	Rat Long-Evans (Female)	3 d	100 mg/g BW/d	Reduction in body weight	LOAEL	Wellman *et al.* 1984
Oral	Cobalt bromide	Rat (Wistar)	1 d	109 mg/ kg BW/ d	Mortality	LD50	Speijers *et al.* 1982
Oral	Cobalt fluoride	Rat (Wistar)	1 d	110 mg/ kg BW/d	Hypothermia	LOAEL	Speijers *et al.* 1982
Oral	Cobalt fluoride	Rat (Wistar)	1 d	110 mg/ kg BW/d	Cardio-vascular	NOAEL	Speijers *et al.* 1982
Oral	Cobalt sulfate	Mouse Swiss-Webster	1 d	123 mg/kg BW/d	Mortality	LD50	Singh and Junnarkar 1991
Oral	Cobalt bromide	Rat (Wistar)	1 d	140 mg/ kg BW/ d	Mortality	LD50	Speijers *et al.* 1982
Oral	Cobalt oxide	Rat (Wistar)	1 d	157mg/ kg BW/d	Hyperemia	LOAEL	Speijers *et al.* 1982
Oral	Cobalt oxide	Rat (Wistar)	1 d	157 mg/ kg BW/d	Hypothermia	LOAEL	Speijers *et al.* 1982
Oral	Cobalt oxide	Rat (Wistar)	1 d	159 mg/ kg BW/d	Mortality	LD50	Speijers *et al.* 1982
Oral	Cobalt chloride	Rat-Sprague-Dawley	1 d	161.1 mg/ kg BW/d	Mortality	LD50	Domingo and Llobet 1984
Oral	Cobalt acetate	Rat (Wistar)	1 d	168 mg/kg BW/d	Mortality	LD50	Speijers *et al.* 1982
Oral	Cobalt fluoride	Rat (Wistar)	1 d	176.6 mg/ kg BW/d	Focal myocardial degeneration	LOAEL	Speijers *et al.* 1982
Oral	Cobalt fluoride	Rat (Wistar)	1 d	176.6 mg/ kg BW/d	Degeneration of proximal tubules	LOAEL	Speijers *et al.* 1982
Oral	Cobalt phosphate	Rat (Wistar)	1 d	187 mg/ kg BW/d	Mortality	LD50	Speijers *et al.* 1982
Oral	Cobalt chloride	Rat (Wistar)	1 d	190 mg/kg BW/ d	Mortality	LD50	Speijers *et al.* 1982
Oral	Cobalt sulfate	Rat (Wistar)	1 d	194 mg/ kg BW/d	Mortality	LD50	Singh and Junnarkar 1991
Oral	Cobalt sulfate	Rat	7 d	279 mg/ kg BW/d	Mortality	LD50	Llobet *et al* (1983)

Route of Exposure	Compound	Species	Duration of Exposure	Dose	Response	Response Level	Reference
Oral	Cobalt oxide	Rat (Wistar)	1 d	795 mg/ kg BW/d	Hemorrhage	LOAEL	Speijers *et al.* 1982
Dermal	Cobalt chloride	Rat Fischer-344 (Female)	3 d	3.8 mg/ kg BW/d	Immuno-toxicity	NOAEL	Ikarashi *et al.* 1992
Dermal	Cobalt chloride	Gn. Pig Hartley (Female)	3 d	7.4 mg/ kg BW/d	Immuno-toxicity	NOAEL	Ikarashi *et al.* 1992
Dermal	Cobalt chloride	Rat-Fischer-344 (Female)	3 d	9.6 mg/kg BW/d	Increased proliferation of lymphatic cells	LOAEL	Ikarashi *et al.* 1992
Dermal	Cobalt chloride	Mouse BALB/c (Female)	3 d	10.8 mg/ kg BW/d	Increased proliferation of lymphatic cells	LOAEL	Ikarashi *et al.* 1992
Dermal	Cobalt chloride	Gn. Pig Hartley (Female)	3 d	14.7 mg/ kg BW/d	Increased proliferation of lymphatic cells	LOAEL	Ikarashi *et al.* 1992

2.3.2.2 Chronic toxicity

Table 2-4: Chronic toxicity values for cobalt and related compounds.

Route of Exposure	Compound	Species	Duration of Exposure	Exposure	Response	Response Level	Reference
Inhalation	Cobalt sulfate	Rat	13 weeks	0.11 mg/m^3	Laryngeal squamous metaplasia	LOAEL	NTP 1991
Inhalation	Cobalt sulfate	Rat-Fischer-344	104 weeks	0.11 mg/m^3	Pulmonary fibrosis	LOAEL	NTP 1998
Inhalation	Cobalt sulfate	Mouse B6C3F1	104 weeks	0.11 mg/m^3	Laryngeal metaplasia	LOAEL	NTP 1998
Inhalation	Cobalt sulfate	Mouse B6C3F1 (Female)	104 weeks	0.38 mg/m^3	Alveolar/ bronchiolar adenoma/ carcinoma	LOAEL	NTP 1998
Inhalation	Cobalt sulfate	Rat-Fischer-344 (Female)	104 weeks	0.38 mg/m^3	Alveolar/ bronchiolar Neoplasms	LOAEL	NTP 1998
Inhalation	Cobalt sulfate	Rat	13 weeks	1.14 mg/m^3	Polycythemia	LOAEL	NTP 1991
Inhalation	Cobalt sulfate	Mouse B6C3F1 (Male)	104 weeks	1.14 mg/m^3	Alveolar/ bronchiolar Adenoma/carcinoma	LOAEL	NTP 1998
Inhalation	Cobalt sulfate	Rat Fischer-344	104 weeks	1.14mg/m^3	Alveolar/ bronchiolar neoplasms	LOAEL	NTP 1998

Route of Exposure	Compound	Species	Duration of Exposure	Exposure	Response	Response Level	Reference
		(Male)					
Inhalation	Cobalt sulfate	Rat-Fischer-344 (Female)	104 weeks	1.14 mg/m^3	Pheochromo-cytoma	LOAEL	NTP 1998
Inhalation	Cobalt sulfate	Mouse	13 weeks	1.14 mg/m^3	Decreased sperm motility	LOAEL	NTP 1991
Inhalation	Cobalt Chloride	Guinea Pig	9 weeks	2.4 mg/m^3	Increased lung weight	LOAEL	Camner *et al,* (1993)
Inhalation	Cobalt Oxide	Hamster	life	7.9 mg/m^3	emphysema	LOAEL	Wehner *et al.* 1977
Inhalation	Cobalt Oxide	Hamster	life	7.9 mg/m^3	Body weight	NOAEL	Wehner *et al.* 1977
Inhalation	Cobalt Hydro-carbonyl	Rat	12 weeks	9 mg/m^3	Lung inflammation	LOAEL	Palmes *et al.*, 1959
Inhalation	Cobalt Hydro-carbonyl	Rat	12 weeks	9 mg/ m^3	Increased hemoglobin	LOAEL	Palmes *et al.*, 1959
Inhalation	Cobalt Hydro-carbonyl	Rat	12 weeks	9 mg/ m^3	Body weight	NOAEL	Palmes et al 1959
Inhalation	Cobalt sulfate	Rat	13 weeks	11.4 mg/m^3	Decrease body weight	LOAEL	NTP 1991
Inhalation	Cobalt sulfate	Mouse (Male)	13 weeks	11.4 mg/m^3	Testes atrophy	LOAEL	NTP 1991
Inhalation	Cobalt sulfate	Mouse (Female)	13 weeks	11.4 mg/m^3	Increased length of estrous cycle	LOAEL	NTP 1991
Inhalation	Cobalt sulfate	Mouse	13 weeks	11.4 mg/m^3	Lymph node hyperplasia	LOAEL	NTP 1991
Inhalation	Cobalt sulfate	Rat	13 weeks	11.4 mg/m^3	Increased severity of cardio-myopathy	LOAEL	NTP 1991
Inhalation	Cobalt Chloride	Albino Rats	30 weeks	144 mg/kg	Mortality	LD50	Murdock, H.R., et al (1959)
Oral	Cobalt Chloride	Rat	6 weeks	2.5 mg/ kg BW/d	Polycythemia	LOAEL	Stanley *et al.* 1947
Oral	Cobalt Chloride	Rat (Female)	10 weeks	5 mg/ kg BW/d	Reproductive toxicity	NOAEL	Nation *et al.* 1983
Oral	Cobalt Sulfate	Rat Sprague-Dawley (Female)	24 weeks	8.4 mg/ kg BW/d	Left ventricular Hypertrophy	LOAEL	Haga *et al.* 1996
Oral	Cobalt Chloride	Rat	21 weeks	10 mg/kg BW/d	Necrosis of Renal Tubular Lining Cells	LOAEL	Murdock 1959
Oral	Cobalt Chloride	Rat CFY	3 weeks	12.4 mg/ kg BW/d	Multifocal myocytolysis and	LOAEL	Morvai et al, 1993

Route of Exposure	Compound	Species	Duration of Exposure	Exposure	Response	Response Level	Reference
					degeneration of myofibrilles		
Oral	Cobalt Chloride	Rat CFY	3 weeks	12.4 mg/ kg BW/d	Decreased Body Weight	LOAEL	Morvai et al, 1993
Oral	Cobalt Chloride	Rat (Female)	10 weeks	20 mg/kg BW/d	Testicular atrophy	LOAEL	Nation *et al.* 1983
Oral	Cobalt Sulfate	Gn. Pig	5 weeks	20 mg/kg BW/d	Mortality	LD50	Mohiud-din *et al.* 1970
Oral	Cobalt Chloride	Mouse Parkes (Female)	6 weeks	26 mg/kg BW/d	Necrosis and inflammation of thyroid	LOAEL	Shriv-astava *et al.*, 1996
Oral	Cobalt Chloride	Mouse CD-1 (Male)	13 weeks	43.4 mg/ kg BW/d	Testicular degeneration	LOAEL	Anderson *et al.* 1992
Oral	Cobalt Chloride	Mouse B6C3F1	10 weeks	58.9 mg/kg/d	Reduced fertility	LOAEL	Pedigo *et al.* 1993
Oral	Cobalt Nitrate	Rat	14 weeks	198 mg/ kg BW/d	Mortality	LD50	Llobet, *et al.*, 1983

2.3.3 Toxicity

2.3.3.1 Endocrine toxicity

Cobalt increases erythropoietin *in vitro* and *in vivo* (Fisher and Langston, 1968; Janda *et al.*, 1965, as referenced in Endoh *et al.*, 2000). An *in vitro* study by Goldberg *et al.*, (1987) (as referenced in Endoh *et al.*, 2000) indicated that treatment with cobalt increased production of erythropoietin mRNA in human hepatoma cell lines, Hep3B and HepG2.

2.3.3.2 Reproductive and developmental toxicity

Male B6C3F1 mice treated with cobalt chloride showed a decrease in sperm concentration and motility (Pedigo *et al.*, 1993). Cobalt chloride was also shown to have a negative effect on the structure and function of the testis in golden hamsters (Lukac *et al.*, 2007). The cobalt treatment resulted in significantly reduced volume of the seminiferous epithelium and produced dilated capillaries in the interstitium (Lukac *et al.*, 2007).

Cobalt sulphate was shown to have similar effects on the reproductive system in an NTP inhalation study. The NTP study on F344/N rats and B6C3F1 mice found decreased sperm motility in mice exposed to 3 mg/m^3, and an increase in abnormal sperm in mice exposed to 30 mg/m^3. Mice exposed to 30 mg/m^3 had decreased testis and epididymis weights (NTP 1991).

2.3.3.3 Immunotoxicity

No data were available on the immunotoxicity of cobalt.

2.3.3.4 Neurotoxicity

No data were available on the neurotoxicity of cobalt.

2.3.3.5 Genotoxicity

Tungsten carbide-cobalt (WC-Co) particles were shown to have genotoxic and apoptotic effects in peripheral blood mononucleated cells (Lombaert *et al.*, 2008). An *in vitro* study conducted by Anard *et al.* (1997) demonstrated the clastogenic properties of cobalt in a mixture of cobalt with tungsten carbide in peripheral lymphocytes. Tungsten carbide alone did not cause a significant increase in DNA breaks (Anard *et al.*, 1997).

2.3.3.6 Carcinogenicity

IARC (2006) has classified cobalt metal with tungsten carbide as 'probably carcinogenic to humans' (Group 2A), and cobalt metal alone, cobalt sulfate and other soluble cobalt (II) salts as 'possibly carcinogenic to humans' (Group 2B) (as referenced in Lombaert *et al.*, 2008). Injection animal studies have demonstrated the development of sarcomas at the injection site.

Epidemiological evidence for the carcinogenicity of cobalt is weak (Barceloux, 1999).

2.3.3.7 Other clinical effects

An *in vivo* study using guinea pigs found treatment with cobaltous chloride depressed calcium-dependant regulation of calcium-sensitive potassium conductivity in coronary artery smooth muscle cells (Hristov *et al.*, 2004). Cobalt sulfate fed to male Sprague-Dawley rats over a 24 week period caused a lower rate of mitochondrial ATP production rate in relation to myocardial mass and decreased manganese-superoxide dismutase activity (Clyne *et al.*, 2001).

2.3.4 Human Risk Assessment

The general population is exposed to cobalt primarily through the diet. However occupational exposure occurs through the production of cobalt dust (Barceloux, 1999). Additional agents such as tungsten can modulate the toxicity of cobalt in industrial exposure (Barceloux, 1999). Toxicities associated with excessive cobalt exposure include thyroid dysfunction, a syndrome known as "beer drinker's cardiomyopathy", interstitial pulmonary fibrosis, allergic contact dermatitis, and occupational asthma (Barceloux, 1999).

Table 2-5: Estimated average daily intake levels of cobalt for the general population in different countries.

Country	Estimate of Average Intake Level	Reference
United Kingdom	5-40 µg/d	Jenkins *et al.*, 1980, as referenced in Kim *et al.*, 2006
Canada	11 µg/d 7-14 µg/d - children	Dabeka & McKenzie, 1995, as referenced in Kim *et al.*, 2006
France	29 µg/d	Biego *et al.*, 1998, as referenced in Kim *et al.*, 2006

Table 2-6: Ambient monitoring of cobalt in different workshops

	n	Cobalt (µg/m^3)
Forming	5	0.61-2.82
Pressing	3	0.87-116.0
Powder processing	4	7.9-64.3
Production of tungsten carbide	1	0.39
Sintering	1	343.0
Grinding (wet)	1	0.20
Grinding (dry)	1	0.48
Heavy alloy production	2	0.85-1.84

Reference: Kraus *et al.*, 2001

The American Conference of Governmental Industrial Hygienists (ACGIH) has established an 8-h time-weighted average (TWA) of 0.02 mg/m^3 for occupational exposure. The Occupational Safety and Health Administration (OSHA) has an established TWA of 0.1 mg/m^3, and the National Institute for Occupational Safety and Health (NIOSH) recommends a TWA of 0.05 mg/m^3 (OSHA 2001e; NIOSH 2001; as referenced in ASTDR 2004). The NIOSH has also has established an IDLH (immediately dangerous to life or health concentration) of 20 mg/m^3 (NIOSH 2001, as referenced in ASTDR 2004).

Thyroid dysfunction has been associated with cobalt exposure and has been reported in the treatment of anemia with cobalt compounds (Weaver *et al.*, 1956; Kriss *et al.*, 1955, as referenced in Brock and Stopford, 2003). The association of cobalt exposure and cardiomyopathy was first observed in heavy drinkers, who drank beer that contained 1 to 1.5 mg of cobalt chloride/L (Barceloux 1999; D'Adda *et al.*, 1994; Kennedy *et al.*, 1981). Hard metal lung disease was also associated with cobalt exposure (Zanelli *et al.*, 1994). A study by Linna *et al.*, (2003) did not find an association of cobalt exposure and hard metal lung disease, however there was an association with exposure and occupational asthma. Cobalt is a known allergen that produces asthma and allergic contact dermatitis (Athavale *et al.*, 2007; Macedo *et al.*, 2007; Anavekar and Nixon 2006; Dotterud and Smith-Silvertsen 2007).

2.3.5 Treatments and remediation

There is very little data concerning treatments of cobalt toxicity in humans. The toxicities associated with cobalt are mainly treated supportively (Barceloux 1999).

2.4 ENVIRONMENTAL FATE

2.4.1 Forms

Cobalt is present in nature mostly in the sulphide, arsenide, and oxide forms. It is incorporated into complex minerals in the environment and the mineral ores. The forms with the highest amount of cobalt are cobaltite (CoAsS), erythrite [$Co_3(AsO_4)_2$] and smaltite ($CoAs_2$) (Barceloux, 1999). Cobalt is found incorporated less often with nickel, copper, silver, iron and lead ores, and more often in nickel and copper ores. Consequently, it is a common by-product of nickel and copper mining and smelting, and a large portion of cobalt production is from recovery of cobalt from those mining wastes. However, significant quantities of the minor metals contained in these ores, including cobalt, are also lost or discarded during the refining or smelting process as smoke, dust or slag (Ayres, 1997).

At mining sites, rock without high content of the desired metal are considered to be "waste" and dumped. These metals may still have a significant quantity of other metals. If these metals are in the sulphide form, which is usual in the case of Ni, Cu and Co, acid mine drainage can be a problem (Trois *et al.*, 2007). This is a process whereby the metals are mobilized and solubilized and can enter the environment and bodies of water as a result. The process can occur abiotically following either of the two reactions shown below (Trois *et al.*, 2007).

(Equation 1) $MS + H_2SO_4 + ½\ O_2 \rightarrow MSO_4 + H_2O + S^o$
(Equation 2) $MS + 2Fe^{3+} \rightarrow M^{2+} + 2Fe^{2+} + S^o$

where M is any metal, in this case cobalt, released from the waste pile as acid mine drainage as either cobalt sulphate ($CoSO_4$) or the free cobalt ion Co^{2+}.

2.4.2 Air

Cobalt is present in the air as particulate matter with a mean mass diameter of 2.6 μm (Barceloux, 1999). It originates from both natural and anthropogenic sources nearly equal quantities, with the mining and processing of cobalt containing ores being one of the main anthropogenic sources (Lison, 2005). Near mining extraction and processing activities, cobalt is primarily in the form of cobalt arsenide or cobalt sulphide as a result of the sulphide and arsenide ores in which it is commonly found, or in the form cobalt oxide resulting of combustion (Barceloux, 1999). Cobalt is most often found in nickel and copper ores, and since Cu and Ni are found as sulphides in nature, the smelting process converts these metals to oxides by combustion (Ayers, 1997). The cobalt

incorporated in these metals can also be converted to the oxide form (CoO or Co_3O_4) and released in particulate form into the air as smoke or dust (Barceloux, 1999).

The fate of the cobalt particles is dependent on particle size and density as well as the speciation, although the chemical speciation of cobalt in the air has not yet been fully determined (Lison, 2005). Deposition of the particles on surface waters or soils is primarily determined by wind speed, direction, and precipitation. It has been found that higher levels of cobalt occur in the air after a period of no-rain compared to a period of rain (Hamilton, 1994).

According to the National Pollutant Release Inventory (NPRI, 2008), out of a total 11 tonnes of cobalt released on-site into the air, land, and water at various industries across Canada, 10 tonnes are released into the air. This indicates that, within Canada, air is certainly a major site of cobalt release. These cobalt particulates may then deposit on soils and surface waters, leading to their subsequent contamination. Generally the concentration of cobalt is 1-2 ng Co/m^3 in urban areas, and lower in remote areas (Barceloux, 1999). In highly industrialized urban areas, point source concentration have been measured up to 10 ng Co/m^3 and concentrations as high as 600 ng Co/m^3 have been measured near industrial sources such as nickel mining and smelting operations (Barceloux, 1999).

2.4.3 Soil

The total cobalt that is present in the soils of England and Wales as found by Suttle *et al.* 2003 to range from 5 – 24 mg/kg whereas Lison (2005) reported soil concentrations ranging from 0.1 – 50 μg/kg, illustrating great variability. These amounts reported are the total amount of cobalt in the soils, which is different than the total available cobalt to plants or other organisms. For instance, Suttle *et al.* (2003) and Lison (2005) found that 3-13% and 0.1-2 μg/kg of the total cobalt found was available to plants.

The bioavailability of cobalt is mainly dictated by the pH of the soil in question. It has been found to have a strong negative relationship with pH as well as manganese content. (Suttle *et al.*, 2003). This means that, as the pH increases and the soil becomes more alkaline, the bioavailability of the cobalt decreases to organisms. In addition to pH, many other factors play a role in determining the bioavailability of cobalt in soils including the amount of organic matter, clay mineral content, redox state of the soil, cation exchange capacity of the soil and the organic complexation processes which occur (Hamilton, 1994).

Cobalt that reaches the soil through deposition from diffuse sources, such as deposition of airborne cobalt particles, is strongly incorporated in to the soil. It has been found to migrate slowly down the soil column under ploughed soil conditions, as well as in situations of long term irrigation of intact soil columns (Gal *et al.*, 2007). The dispersion of cobalt down the soil column is related to the soil type as well as the speciation and form of the cobalt in the soil (Gal *et al.*, 2007). The predominant species of cobalt in soils is known to be Co^{3+} (Lison, 2005).

2.4.4 Water

Some of the highest concentrations of cobalt in freshwater come from mine waste waters among other anthropogenic inputs (Hamilton, 1994). As briefly described above, acid mine drainage may include, cobalt as cobalt sulphate ($CoSO_4$), or the free cobalt ion Co^{2+} (Trois *et al.*, 2007).

Cobalt binds strongly to sediments, and is removed from the water column through this process. Diamond (1992) conducted a laboratory study investigating the removal of cobalt from a water column with freshwater, and determined it was approximately exponential, with a half-life of 25 d. In addition, a whole-lake experiment conducted by Hesslein and Broecker (1980) found a similar result; that the half-life for cobalt within the water column was between 15 and 30 d.

If the pH of the sediment is outside of the range of 3-9, dissolved cobalt will be held within the water column through the binding to dissolved natural organic substances, which are later transported and deposited in coastal seawater. As a result, coastal seawaters generally have a higher concentration of cobalt that open seawaters (Hamilton, 1994). Cobalt has been detected in drinking water in a range of concentrations from 0.1 – 5 μg/L, and in the open ocean at an average concentration of 0.3 μg/L (Barceloux, 1999).

2.5 ENVIRONMENTAL HEALTH ASSESSMENT

2.5.1 Toxicological data

2.5.1.1 Aquatic Organisms

The aquatic toxicity data presented below are data for cobalt chloride ($CoCl_2$) exclusively, as elemental cobalt is insoluble and consequently few aquatic studies have been conducted using elemental cobalt. Diamond (1992) showed that the dissociated $CoCl_2$ in water was between 73.8% and 112.2% of the total cobalt, indicating that $CoCl_2$ is readily dissociated. Therefore the toxicity values presented in Table 2-5 represent the Co^{2+} ion of dissociated $CoCl_2$.

Table 2-7 below shows *Daphnia magna* and *Oncorhynchus mykiss* to be the most sensitive species. For other metals, daphnids are often the most sensitive species, with fish being less sensitive and plants less sensitive than fish (Diamond, 1992). However, these trends do not hold true for cobalt. The fish, *Oncorhynchus mykiss* and *Pimephales promelas* were found to be more sensitive than *Daphnia magna* (Diamond 1992).. A possible explanation for this is the influence that cobalt has on the formation of blood, leading to an excess of red blood cells, which may occur in fish but not invertebrates (Diamond, 1992). However, this does not explain the difference in sensitivity between *Oncorhynchus mykiss* and other fish species.

Toxicity data for cobalt were obtained from the USEPA ECOTOX Database (USEPA, 2008). Only data with LC50 as an endpoint were reported in this text. The acute to chronic ratios (ACR) for three aquatic invertebrates are shown in Table 2-7 which can be used to convert acute data to chronic data.

Table 2-5: Acute toxicity data of 96-h cobalt chloride ($CoCl_2$) exposure to aquatic organisms

Species	**Common name**	**96-h LC_{50} (mg/L)**
Amphibians		
Xenopus laevis	African clawed frog	10.4
Rana hexadactyla	Frog	17.6
Crustaceans		
Daphnia magna	Water flea	1.5
Diaptomus forbesi	Calanoid copepod	3.4
Austropotamobius pallipes pall	Crayfish	8.8
Asellus intermedius	Aquatic sowbug	50
Gammarus fasciatus	Scud	50
Fish		
Oncorhynchus mykiss	Rainbow trout	1.4
Pimephales promelas	Fathead minnow	22
Colisa fasciata	Giant gourami	102
Cyprinus carpio	Common carp	333
Molluscs		
Helisoma trivolvis	Ramshorn snail	50
Worms		
Dugesia tigrina	Turbellarian, flatworm	12
Lumbriculus variegatus	Oligochaete	50
Branchiura sowerbyi	Oligochaete	1330

Table 2-6: Acute to chronic ratios (ACR) for various aquatic invertebrates

Species	**ACR**
Pimephales promelas	1.01
Ceriodaphnia dubia	> 46.9
Daphnia magna	111

Reference: Diamond, 1992

2.5.1.2 Terrestrial organisms

Cobalt is an essential element for mammals as part of the vitamin B_{12} complex, and cobalt deficiency in mammals can lead to anemia and nervous system problems (Barceloux, 1999). Although not shown with certainty, there is also evidence that cobalt has a positive effect on the growth of non-leguminous plants such as cereals (Gal *et al.*, 2007). However, the quantity of terrestrial invertebrate toxicity data is very limited. The USEPA ECOTOX Database (USEPA, 2008) was used to obtain EC20 values for plants, listed in Table 2-7.

In general, plants accumulate small amounts of cobalt. With the exception of select cobalt hyperaccumulating strains, the bioconcentration factor (BCF) is less than 0.5.

Cobalt accumulates in the fruit, grains and seeds of plants, the parts that are most often consumed (Gal *et al.*, 2007).

Birds and mammals are exposed to cobalt by ingesting soil during feeding or preening, or through the ingestion of plants that contain cobalt. Plants and soil invertebrates are exposed through direct contact with the soil, or through direct contact and ingestion of the soil, respectively (Gal *et al.*, 2007). Consequently, a major route of cobalt toxicity for terrestrial mammals is secondary poisoning, through ingestion of cobalt-containing plants (Gal *et al.*, 2007).

Table 2-7: Chronic toxicity data of cobalt exposure to terrestrial organisms

Species	Common name	Endpoint	Exposure duration (d)	Value (mg/kg)	Response description	Source
Invertebrates						
Folsomia candida	Springtail	EC50	28	409	Decreased reproduction	Lock *et al.*, 2004
Folsomia candida	Springtail	EC50	28	1480	Decreased reproduction	Lock *et al.*, 2004
Plants						
Raphanus sativus	Radish	EC20	14	6.55-266	Decreased shoot growth	(USEPA, 2008)
Medicago sativa	Alfalfa	EC20	14	6.12- 281	Decreased shoot growth	(USEPA, 2008)
Hordeum vulgare	Barley	EC20	14	6.74-294	Decreased shoot growth	(USEPA, 2008)
Medicago sativa	Alfalfa	EC20	14	6.12-281	Decreased seedling emergence	(USEPA, 2008)
Hordeum valgare	Barley	EC20	14	6.74-295	Decreased seedling emergence	(USEPA, 2008)
Raphanus sativa	Radish	EC20	14	6.55-275	Decreased seedling emergence	(USEPA, 2008)
Raphanus sativa	Radish	EC20	14	6.55-275	Mortality	(USEPA, 2008)
Hordeum vulgare	Barley	EC20	14	6.74-295	Mortality	(USEPA, 2008)
Medicago sativa	Alfalfa	EC20	14	10.25 - 269	Mortality	(USEPA, 2008)

2.5.2 Environmental risk assessment

Some of the highest amounts of cobalt in the environment are as a result of mining and smelting, and in general, these values are not a major concern for the most parts of the environment. Concentrations that occur in water are well below those that cause acute effects in aquatic organisms. Concentrations of cobalt in soil are highly variable and can be found to be above levels which may have an effect on terrestrial organisms.

The bioavailability of cobalt in soil to organisms is based on multiple characteristics of the soil. The concern for cobalt toxicity in the environment should be focused on those soil that are known to have a high amount of bioavailable cobalt soil, in addition to the immediate impact of acid mine drainage on receiving waters.

2.5.3 Treatments and remediation

Concentrations of cobalt can be decreased in water through sulfide precipitation and adsorption to sediments and particles (von der Heyden, 2004). Metal adsorption is pH dependent, and decreasing the pH of the soil, particularly in the critical region from 4.5 to 5, can result in a significant increase in concentrations of soluble metal. Therefore, the addition of limestone to raise the pH of water having a low pH due to acid mind drainage can reduced the amount of soluble cobalt (von der Heyden, 2004).

Cobalt concentrations in soil can be decreased by two basic methods; removal of the cobalt from the soil and decreasing the bioavailability of the soil. The first can be achieved through phytoremediation, where plants that are able to accumulate cobalt in high concentrations on the contaminated soil are removed. Some plant species that are known cobalt hyperaccumulators are *Aeollanthus subacaulis* var. *ericoides* and *Senecio* cf. *coronatus*, which are reported to be able to accumulate up to 4129 mg Co/kg dry weight (Baker and Brooks, 1989). A reduction in bioavailability of cobalt in soil can be achieved by increasing the pH. Adsorption of Co^{2+} in soil colloids remains between a pH of 6 to 7, but much lower at a reduced pH (Gal *et al.*, 2007).

As well, since manganese and iron can bind with cobalt to form less biologically active species, thus the addition of Mn or Fe could reduce the total available cobalt. An increase in the soil organic matter and clay minerals could also have this effect (Gal *et al.*, 2007). Poorly drained soils also have higher amounts of bioavailable cobalt; therefore maintaining proper drainage of agricultural fields could reduce the amount of cobalt taken up by the plants (Hamilton, 1994).

2.6 CONCLUSIONS

Cobalt occurs naturally in rocks, soil, and has a role in human nutrition as part of vitamin B12 (Kim *et al.* 2006). Humans are often exposed to cobalt through ores, fertilizers, and during the refining of metals (ATSDR 2004; Kim *et al.* 2006). Cobalt is found in the air, water, and soil where its bioavailability can affect its toxicity to organisms. Cobalt may also accumulate in the fruits, grains, and seeds of many plants. However, concentrations are often well below those causing adverse effects in terrestrial species (Gal *et al.*, 2007). Cobalt has tested positive for reproductive toxicity (Lukac *et al.*, 2007), genotoxicity (Anard *et al.*, 1997), and carcinogenic activity (IARC, 2006). In addition, case reports have linked cobalt exposure with several negative outcomes, including allergic contact dermatitis. It is for this reason that the release of cobalt and its compounds should be controlled (Athavale *et al.*, 2007; Macedo *et al.*, 2007; Anavekar and Nixon 2006; Dotterud and Smith-Silvertsen 2007). However, reports of effects on humans and ecosystems are limited to occupational and extremely high exposures (Suttle *et al.*, 2003). At the present time, it appears that the general population is not at risk to cobalt toxicity.

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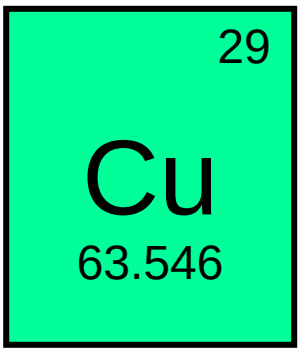

3.1 IDENTITY

Symbol: Cu

CAS No.: 7440-50-8

Electron configuration: [Ar] $3d^{10}$ 4s

3.2 CHARACTERISTICS

3.2.1 Physical and chemical properties

Table 3-1: Physical and chemical properties of copper

Atomic number	29
Atomic mass	63.546 g/mol
Oxidation states	+1, +2, +3, +4 (mildly basic oxide)
Major Isotopes	^{63}Cu, ^{65}Cu
Boiling point	2835 K
Melting Point	1357.77 K
Ionization energies	1st: 745.5 kJ/mol 2nd: 1957.9 kJ/mol 3rd: 3555 kJ/mol
Electron affinity	119 kJ/mol
Electronegativity	1.90 (Pauling scale)
Density	8.96 g/cm^3
Physical description	Lustrous reddish brown metal

Reference: ATSDR, 2004

3.2.2 Sources

Endogenously, copper is found in enzymes of the ferroxidase family, specifically ceruloplasmin, which facilitates iron transport in the blood (Health Canada, 1992). As copper has the ability to participate in redox reactions, copper is found in many enzymes. Enzymes that include copper as a structural element include: tyrosinase, cytochrome C oxidase, ascorbic acid oxidase, amine oxidase, and superoxide dismutase (Health Canada, 1992). Copper is essential for the formation of hemoglobin (ATSDR, 2004).

Copper exposure can occur through a variety of vectors, most commonly in foodstuffs, drinking water, through dermal contact, and through inhaled air. Foods known to be rich in copper include: nuts, meats, dairy products, green leafy vegetables, fruits, and shellfish (Health Canada, 1992). Elevated levels of copper can be found in drinking water in Canadian homes if copper piping is present. This is because copper is able to leach from

the pipes if the water within them is stagnant (ATSDR, 2004). Elevated concentrations of copper in lakes and rivers can occur if they have been treated with copper sulfate fungicides or pesticides employed to control algae and fungi, or if they receive cooling water from power plants or copper mines with elevated copper levels (ATSDR, 2004).

There are over 72 known copper-containing minerals, of which can be divided into copper oxides and copper sulfides; the oxide form being more economical and sought after for processing (Edelstein, 2007). Copper ores are commonly found in igneous and metamorphic rock formations.

Table 3-2: Annual releases of copper into the environment in Canada

Province	**On-site Releases (tonnes)**				**Number of Sites***
	Air	Water	Land	Total	
Saskatchewan	0	0	0	0.214	10
Quebec	72.639	32.045	50	155.283	81
P.E.I.	0	0	0	0	0
Ontario	192.582	27.563	126	349.163	306
Nunavut	0	0.001	0	0.001	1
Nova Scotia	0.007	0.138	0	0.15	6
Newfoundland	0.146	11	0	11.46	2
New Brunswick	0.708	0.561	38	39.269	7
Manitoba	105.173	2.815	8.6	117.126	20
British Columbia	19.866	23.012	3.1	46.492	38
Alberta	1.632	1.944	58.017	61.623	35
Canada (total)	393	100	285	783	507

* industrial sites Reference: NPRI, 2008

3.3 MAMMALIAN HEALTH ASSESSMENT

3.3.1 Toxicokinetics/ toxicodynamics

3.3.1.1 Absorption, distribution, metabolism, excretion

Copper is absorbed from the intestinal mucosa by diffusing through the mucous layer lining the walls (Linder, 1996). The absorption of copper appears to be inversely related to the amount of copper in the gastrointestinal tract (Strickland *et al.*, 1972; Turnland *et al.*, 1989). Because copper is a highly controlled element in the body, simple diffusion could easily lead to excess levels. A high affinity copper transporting protein, known as human copper transporter 1 (hCtr1), is responsible for managing copper absorption (Zhou and Gitschier, 1997). Expressed by all tissues of the body, hCtr1 shows highest levels of expression in the heart, liver and pancreas, median levels in the intestine, and lowest levels in the brain and skeletal muscle (Zhou and Gitschier, 1997). The transporter facilitates Cu^{+1} ion transport into enterocytes, while the Menkes ATPase (or P-type ATPase) controls Cu^{+1} export into the portal circulation (Murata *et al.*, 1997). Defects in the Menkes ATPase result in copper accumulation in cells bordering the basement membranes of the intestines, glomerulus, and vasculature of the blood-brain barrier (Danks *et al.*, 1973). Functioning Menkes proteins allow copper to enter the bloodstream.

Once in the portal circulation, free Cu^{+1} ions are quickly bound to circulating albumin and histidine (Linder, 1996). Upon reaching the liver, it is believed that the Cu^{+1} ions are transferred from albumin or histidine, to hCtr1 located on the hepatocyte surface and taken into the cell (Linder, 1996). Within the hepatocyte, copper is distributed to the various enzymes in which it is required, and any excess is bound to ceruloplasmin (Holmberg and Laurell, 1948). Capable of binding seven copper atoms (Sato and Gitlin, 1991), ceruloplasmin is the major transporter of this metal within the vasculature, carrying upwards of 95% of serum copper (Holmberg and Laurell, 1948). Despite the large capacity of ceruloplasmin to transport Cu^{+1}, its absence due to congenital defects, bears no detrimental effects on copper levels in peripheral tissues. This suggests that albumin and histidine transport of Cu^{+1} is sufficient (Harris *et al*., 1998). Copper that has been incorporated into the cell through the hCtr1 transporter is removed from the protein and bound to the chaperone protein Atx1, one Cu^{+1} ion at a time (Lin and Culotta, 1995; Lin, 1997). Metallothionein is another intracellular copper chaperone protein and is responsible for the storage of unused copper (Wake and Mercer, 1985). Cupric ions are distributed to various copper-dependent enzymes and proteins within the cell including: cytochrome c oxidase, lysl oxidase, monoamine oxidase, copper-zinc superoxide dismutase and ceruloplasmin (Davis and Mertz, 1987). Any additional copper that is not incorporated into an enzyme or associated with ceruloplasmin is sequestered within a vacuole bound to metallothionein for storage (Edie *et al.*, 1993).

Biliary secretion of copper is the predominant mode of excretion and accounts for the removal of approximately 72% of copper in humans (Bush *et al.*, 1955). Biliary copper is bound to both small molecular weight and macromolecular species (Gollan and Dellar, 1973) and has insignificant reabsorption (Farrer and Mistilis, 1967). The remaining 28% of copper excretion occurs from unabsorbed copper and sloughed enterocytes being excreted in the fecal matter. Copper can be excreted into the urine, but under normal circumstances only accounts for 0.5-3.0% of daily copper intake (Cartwright and Wintrobe, 1964).

3.3.1.2 Cellular Interactions

Because of copper's ability to undergo redox reactions, it can generate reactive oxygen species (ROS) through Fenton chemistry (Held *et al.*, 1996). This occurs particularly with excess of unbound copper in cells. These ROS have the potential to form adducts with cellular structures, including proteins and DNA, and can result in defective proteins and mutations. Copper also plays an essential role in many enzymes as an electron transporter. For example, copper is an essential cofactor for lysl oxidase, an enzyme essential for collagen synthesis, and for cytochrome c oxidase, an enzyme involved in mitochondrial respiration (Tapiero *et al.*, 2003) Just as free copper can generate ROS, bound copper to the enzyme superoxide dismutase can extinguish existing ROS (Davis and Mertz, 1987).

3.3.2 Toxicological Data

3.3.2.1 Acute Toxicity

Table 3-3: Acute toxicity data for copper exposure to mammals

Route of exposure	Species	Level of exposure	Length of exposure	Effect	Source
Oral	Mouse	24 mg Cu/kg/d as copper sulfate	2 weeks	NOAEL	NTP, 1993
Oral	Rat	44 mg Cu/kg/d As copper sulfate	N/A	Hyperplasia of the forestomach mucosa	NTP, 1993
Oral	Rat	133 mg Cu/kg/d	1 week	LOAEL Increased mortality	Boyden *et al*., 1938.
Oral	Rat	200 mg Cu/kg/d	2 weeks	LOAEL Droplets in proximal tubule lumen	Haywood *et al*., 1985b
Oral	Rat	300 mg Cu/kg/d as copper sulfate	1-2 weeks	LOAEL Parenchymal cell hypertrophy	Haywood, 1980
Oral	Rat	550 mg Cu/kg/d	2-15 weeks	LOAEL Increased mortality	Haywood, 1985
Oral	Rat	>550 mg Cu/kg/d	More than 5 weeks	Liver permanently overloaded and chronic hepatitis developed.	ATSDR, 2004
Oral	Swine	750 µg/g diet	N/A	Hypochromic microcytic anemia, jaundice, and marked increases in liver and serum copper levels	Health Canada, 2002
Oral	Mouse	390 or 520 mg/kg/d	1 month	fetal mortality and decreased litter size	WHO
Inhalation	Mouse	0.12–0.13 mg Cu/m^3 as copper sulfate	3 h/d , 5 d/week for 1–2 weeks	Respiratory effects and impaired immune	Drummond *et al*., 1986
Inhalation	Mouse	3.3 mg Cu/m^3 as copper sulfate	single 3-h exposure	Respiratory effects and impaired immune	Drummond *et al*., 1986

3.3.2.2 Chronic Toxicity

Table 3-4: Chronic toxicity data for copper exposure to mammals

Route of exposure	Species	Level of exposure	Length of exposure	Effect	Source
Oral	Rat	4.2 mg Cu/kg/d as copper gluconate	850 d	14.7% decrease in lifespan	Massie and Aiello, 1984
Oral	Rat	14 mg Cu/kg/d as copper carbonate	15 weeks	Increased systolic blood pressure	Liu and Mederios, 1986
Oral	Mouse	42.5 mg Cu/kg/d as copper gluconate	Lifetime	12.8% decrease in maximum lifespan	Massie and Aiello, 1984

3.3.3 Toxicity

3.3.3.1 Endocrine Toxicity

No reports of endocrine-mediated toxicity of copper were found in the literature.

3.3.3.2 Reproductive and Developmental Toxicity

There is a limited amount of published literature investigating the role of copper on reproduction in humans. Of those available, none have observed any reproductive changes or problems associated with copper (Aulerich *et al*., 1982; NTP 1993). However, copper ingested orally by rats and mice has been shown to result in impaired growth (Haddad *et al*., 1991; Lecyk 1980).

3.3.3.3 Immunotoxicity

Immunotoxicity information is limited, but some studies have described copper as a human allergen. There have been cases of the development of allergic contact dermatitis following topical exposure (Barranco, 1972; Saltzer and Wilson, 1968). *In vivo* mice studies have reported adverse alterations to immune functions after inhaling copper sulfate, or ingesting copper chloride and copper sulfate (Drummond *et al*., 1986; Pocino *et al*., 1991; Pocino *et al*., 1990).

3.3.3.4 Neurotoxicity

There were no reports on the neurotoxic effects of copper found in the literature.

3.3.3.5 Genotoxicity

No human genotoxicity data is available, however animal studies have suggested that copper may act as a clastogen (Agarwal *et al*., 1990; Bhunya and Jena, 1996; Bhunya and Pati, 1987; Sideris *et al*., 1988).

3.3.3.6 Carcinogenicity

There were no reports of carcinogenic effects of copper found in the literature. Although carcinogenicity has not been extensively reviewed, the information currently available does not suggest that copper or its salts are carcinogenic (WHO, 1992).

3.3.3.7 Teratogenicity

There were no data available for the teratogenicity of copper in the literature.

3.3.3.8 Gastrointestinal Toxicity

At high exposures, unbound copper can be toxic, resulting in nausea, vomiting, diarrhea, kidney damage, hemolytic anemia, and even death (Merck, 2008). Gastrointestinal disturbances (mainly nausea) are the acute effects seen from high levels of copper in drinking water (Araya *et al*., 2004).

3.3.3.9 Hepatotoxicity

Chronic exposure may lead to copper accumulation in the liver causing liver damage (Araya *et al*., 2004). Inherited copper toxicity, or Wilson's disease, occurs when the liver cannot excrete copper into the bile. This leads to accumulation of copper in the liver (resulting in hepatitis and cirrhosis), as well as the accumulation of copper in the bloodstream and other tissues including the brain and eyes (Merck, 2008).

3.3.4 Human Risk Assessment

Copper is an essential trace element to humans, meaning an appropriate intake is required to maintain good health. There are homeostatic mechanisms in place to regulate absorption, distribution, metabolism and excretion of copper for the maintenance of essential functions (Stern, 2007). Copper has a "U-shaped" dose-response curve, indicating that toxic effects occur with deficient as well as excessive amounts (Stern, 2007).

Increased susceptibility to copper toxicity is seen in individuals suffering from Wilson's disease, infants, and individuals with impaired liver function. Individuals with Wilson's disease are more susceptible to copper toxicity due to improper copper homeostasis. Infants under one year of age do not have fully functioning homeostatic mechanisms for clearing excess copper, and high levels of copper can induce hepatosplenomegaly (Muller-Hocker *et al*., 1988 as cited by ATSDR). As well, individuals with impaired liver function can have an increased susceptibility to copper toxicity from improper storage and secretion of copper, as well as impaired ceruloplasmin synthesis (ATSDR, 2004).

Table 3-5: WHO recommended dietary intakes for copper.

Population	RDI (mg/d)
Infants	0.60
Children (6-10 years)	0.75
Adult males	1.35
Adult females	1.15

Reference: WHO, 1996

The NOEL for copper in drinking water from pooled data from Chile, USA and Northern Ireland was found to be 4 mg/L. The corresponding LOAEL was 6 mg/L, with nausea being the adverse effect observed (Araya *et al*., 2001). The Tolerable Upper Intake Level is 10 mg/d with liver damage as an adverse effect. The WHO provisional guideline for copper in drinking water is 2 mg/L. The Occupational Safety and Health Administration permissible exposure limit (PEL) for copper fumes is 0.1 mg/m^3 and 1 mg/m^3 for copper dust (Cant and Legendre, 1982).

Total copper exposure for the average adult from all sources (including air, drinking water and food) is estimated at 2.75 mg/d (ATSDR, 2004). Higher copper intake in the general population may be a result of ingestion of tap water containing a high concentration of copper. This can be from faulty distribution systems, drinking water sources contaminated with mine drainage, or just naturally high copper concentration in the area. It was found that copper industry emissions in Europe led to an additional intake of 0.25 mg/d of copper from food produced in neighboring areas (Sadhra *et al*., 2007).

In the Unites States it was estimated that up to 505,982 workers were occupationally exposed to excess copper (NIOSH, 1988 as cited by ATSDR, 2004). There are differing views on whether copper exposure in an industrial setting has a negative impact on human health (Weir, 1979 and Borak *et al*., 2000). It has been suggested that copper dust and fumes lead to a condition called metal fume fever (MFF), an acute, self-limited, inflammatory lung disorder generated from the inhalation of metal oxide particles less than 1 μm in size. Symptoms include fever, chills, headache, nausea, vomiting, myalgia, dry cough, chest pain, dyspnea and a metallic taste in the mouth (Borak *et al*., 2000). There have been several reported cases of employees complaining of similar symptoms when working with copper (Gleason, 1967; Armstrong *et al*., 1983 as cited by Borak *et al*., 2000). In one example, copper dust in the employee's breathing zone was measured to be 120 $\mu g/m^3$ (below the PEL), yet symptoms similar to MFF were observed (Gleason, 1967). With the addition of exhaust ventilation, copper dust exposure decreased and MFF-like symptoms disappeared (Gleason, 1967).

An industrial hygiene study of a western US copper smelter and arsenic trioxide production facility found airborne copper particulate levels to range from non-detectable to 3.460 mg/m^3, with a mean of 0.164 mg/m^3 (n = 283). Although some employees had particularly high exposures, most were exposed to levels below the PEL (Cant and Legendre, 1982).

Table 3-6. Sources of copper exposure, the recommended maximum exposure values and actual exposures for the average human and industrial workers.

Copper exposure source	Maximum exposure value	Average human exposure	Industrial human exposure	Reference
Food	10 mg/d	2 mg/d	N/A	Health Canada, 2002
Drinking Water	2 mg/L	0.08 mg/L	N/A	Health Canada, 2002
Inhalation	0.1 mg/m^3	600 µg/d	0.120 mg/m^3	Gleason, 1967
	1 mg/m^3		Non-detectable to 3.460 mg/m^3	Cant, 1982

3.3.5 Treatments and Remediation

With excessive copper exposure, drugs that bind and sequester copper can be effective. Several drugs, including penicillamine have been found to be very effective (Merck, 2008).

Occupational over- exposure, as occurs in industries such as mining and agriculture, is controlled primarily though the implementation of exposure control programs as a means of resolving the problem. Engineering controls at the contaminant source can reduce the amount of copper released into the nearby environment. The use of personal protective equipment should also be enforced, particularly respiratory protection. Continuous exposure and biological monitoring of employees is crucial in order to evaluate the effectiveness of exposure control programs, as well as identifying high risk positions. Employee training emphasizing personal hygiene and safety is also important.

3.4 ENVIRONMENTAL FATE

3.4.1 Air

Copper can be dispersed aerially during the smelting process or during wind erosion of mine tailings (Wilson and Pyatt, 2007). Dispersion of metals is more likely during warm seasons (Wilson *et al*., 2005) and occurs mainly downwind of the mine tailings (Wilson and Pyatt, 2007). Aerial dispersion of metals tends to decrease exponentially moving away from the tailings due to dry deposition and rain-out (Wilson and Pyatt, 2007). There is generally very little information specific to aerial dispersion of copper from mining operations.

3.4.2 Soil

Copper mobility in soil is primarily determined by leaching and adsorption to soil particles (Chaturvedi *et al*., 2007). Copper is thought to bind with carboxyl, hydroxyl and phenol groups of soil particles, with binding of copper to clay particles being increased by organic acids in the soil (Chaturvedi *et al*., 2007). Copper preferentially binds organic material in soil, but can also be bound to manganese and iron oxides, with maximum retention in soil occurring between pH 5 and 7 (Chaturvedi *et al*., 2007).

Generally, there is a greater amount of information on the environmental fate of copper in water from mining waste sites than the fate of copper in soil.

3.4.3 Water

Free copper concentrations in aquatic environments are generally considered to be a function of water pH and the availability of ligands for binding copper (Yun *et al*., 2001). The most common form of copper found in aquatic environments is the cupric ion, Cu^{+2} (Eisler, 1998). In riverine systems, the concentration of the cupric ion is greatest directly after the pond tailings and decreases moving away from the tailings (Yun *et al*., 2001). Copper concentrations in water near mining impacted sites can range from levels below detection to greater than 200,000 µg/L (Table 3-7). This decrease in concentration is due to increasing amounts of clean tributary water and the formation of copper complexes with organic and inorganic species (Yun *et al*., 2001). Copper can also be reduced in highly saline water, such as seawater (Eisler, 1998). Copper forms complexes with organic material, and decreases in copper ion concentrations correlate to increases in dissolved organic content of receiving waters (Martin and Goldblatt, 2007). Hard water is also important for the formation of complexes with the cupric ion, as the most common complexes found in freshwater are formed with carbonate ions above pH 6. These conditions precipitate copper out of solution at high concentrations (Eisler, 1998). Copper can also be precipitated out of solution by being co-precipitated with iron hydroxides; which are formed at neutral to high pH and are caused by the mixing of drainage water with tributary water (Lee and Faure, 2007). The precipitation and binding of copper to organic matter causes an increase in total sediment copper concentrations (Lee and Faure, 2007), while simultaneously decreasing dissolved copper ion concentrations in the water (Yun *et al*., 2001).

Table 3-7: Concentrations of copper at some contaminated sites.

Site	Media	Concentration Range	Source
Chonam-ri Creek, South Korea	Fresh to saltwater	ND-2,810 µg/L	Yun *et al*., 2001
St. Lawrence River, Canada	Sediment	10-1,050 mg/kg DW	Desrosiers *et al*., 2008
Burra Burra and North Potato Creek Watersheds, USA	Freshwater	ND-53,000 µg/L	Lee and Faure, 2007
East Lake, Canada	Freshwater	50 µg/L	Martin and Goldblatt, 2007
Zawar Zinc Mine, India	Tailings	186.23 mg/kg	Chaturvedi *et al*., 2007
Parys Mountain, UK	Soil	<LOD-1,569.9 mg/kg	Wilson and Pyatt, 2007
Britannia Mine, Canada	Waste Rock	93.056-1,783.2 mg/kg	Wilson *et al*., 2005
	Freshwater	<LOD-0.2996 mg/L	
Bucim Mine, Macedonia	Freshwater	50.5-200.4 mg/L	Jordanov *et al*., 2007
Chesapeake Bay Basin, USA	Saltwater	<LOD-160 µg/L	Hall *et al*., 1997
Nopiming Provincial Park, Canada	Tailings	2,000 mg/kg	Ibrahim and Goh, 2001

LOD = limit of detection, ND = not detected, DW = dry weight of sediment or soil

3.5 ENVIRONMENTAL HEALTH ASSESSMENT

3.5.1 Toxicological Data

3.5.1.1 Aquatic Organisms

Copper is an essential nutrient for many aquatic animals, and its uptake and metabolism are tightly regulated (Desrosiers *et al*., 2008). Toxicity caused by copper deficiency is rare or non-existent in aquatic invertebrates (Eisler, 1998). Aquatic animals exposed to copper can have gill damage, disruption of osmoregulation, reduced growth and altered energetic processes (Eisler, 1998). In aquatic macrophytes, copper can reduce photosynthetic processes (Eisler, 1998). Copper can also cause reduced cellular function by interfering with enzymatic activities and can cause reduced resistance to infections and parasites (Eisler, 1998).

Aquatic macrophytes and invertebrates accumulate copper in their tissues, while accumulation in fish varies widely from species to species (Eisler, 1998). Copper has been reported to not accumulate in invertebrates (Desrosiers *et al.* 2008). This is possibly due to biotic regulation, which suggests that accumulation may be case-dependent. In order to obtain chronic values, acute-to-chronic ratios can be used for some of the specific genera (Table 3-8), or a general ratio of 2.8 used for freshwater species (Brix *et al*., 2001). For saltwater species, an acute-to-chronic ratio of 1.3 has been used in Hall *et al.* (1997).

Table 3-8: Acute-to-chronic ratio (ACR) values for selected species from Brix *et al.* (2001).

Species	ACR
Daphnia magna	2.4
Gammarus pseudolimnaeus	3.3
Oncorhynchus tshawytscha	4.5
Pimephales promelas	11.2
Lepomis macrochirus	38.0

Reference: Brix *et al.* (2001)

The 96-h LC50 values for species found in the ECOTOX Database (USEPA, 2008), are summarized in Table 3-9. The most sensitive species indicated in this table is the tubificid worm, *Tubifex tubifex*. Aquatic toxicity data from the ECOTOX Database (USEPA, 2008) were obtained and screened to remove any values that were not LC50s; all concentrations were changed to µg/L and multiple values were averaged with a geometric mean.

Table 3-9: Acute toxicity values of aquatic species at 96-h.

Species	Common Name	96 h LC50 (µg/L)
Crustaceans		
Tigriopus californicus	Harpacticoid Copepod	0.24
Daphnia lumholzi	Water Flea	9.4
Penaeus chinensis	Fleshy Prawn	18
Eurytemora affinis	Calanoid Copepod	23
Acartia tonsa	Calanoid Copepod	37

Species	Common Name	96 h LC50 (µg/L)
Gammarus pulex	Scud	37
Balanus improvisus	Barnacle	100
Amphiascus tenuiremis	Hapracticoid Copepod	125
Ceriodaphnia dubia	Water Flea	130
Macrobrachium rosenbergii	Giant River Prawn	149
Paratya australiensis	Shrimp	158
Americamysis bahia	Opossum Shrimp	181
Gammarus lacustris	Scud	212
Cypris subglobosa	Ostracod	277
Penaeus merguiensis	Banana Prawn	380
Gammarus sp.	Scud, Amphipod	910
Carcinus maenas	Green Crab	51,800
Fish		
Oncorhynchus tshawytscha	Chinook Salmon	48
Etroplus maculatus	Pearlspot	50
Gambusia affinis	Western Mosquitofish	56
Chrysophrys major	Red Sea Bream	70
Oncorhynchus kisutch	Coho Salmon	88
Oncorhynchus mykiss	Rainbow Trout	96.7
Cirrhinus mrigala	Carp	110
Poecilia reticulata	Guppy	124
Salmo salar	Atlantic Salmon	125
Osteichthyes	Bony Fish	130
Menidia beryllina	Inland Silverside	203
Morone saxatilis	Striped Bass	310
Channa punctata	Snake-head Catfish	362
Cyprinodon variegatus	Sheepshead Minnow	368
Sciaenops ocellatus	Red Drum	518
Barbus gonionotus	Silver Barb	530
Cyprinus carpio	Common Carp	621
Ictalurus punctatus	Channel Catfish	732
Tilapia mossambica	Mozambique Tilapia	800
Fundulus diaphanus	Banded Killifish	840
Catostomus commersoni	White Sucker	886
Lepomis macrochirus	Bluegill	1,250
Pimephales promelas	Fathead Minnow	1,506
Pagrus major	Red Sea Bream	1,991
Liza vaigiensis	Square Tail Mullet	2,600
Lepomis gibbosus	Pumpkinseed	2,700
Gambusia affinis affinis	Mosquitofish	2,770
Priopidichthys sp.	Plain-head Perchlet	3,353
Mugil sp.	Mullet	4,250
Anguila rostrata	American Eel	6,000
Morone americana	White Perch	6,400
Insects		
Chironomus sp.	Midge	30
Chironomus tentans	Midge	452

Species	Common Name	96 h LC50 (µg/L)
Chironomus riparius	Midge	920
Chironomus plumosus	Midge	1,226
Invertebrates		
Hydra viridissima	Hydra	25
Strongylocentrotus intermedius	Sea Urchin	30
Hydra vulgaris	Hydra	49
Stichopus sp.	Sea Cucumber	70
Hydra oligactis	Hydra	84
Pectinatella magnifica	Bryozoa	140
Plumatella emarginata	Bryozoa	140
Lophopodella carteri	Bryozoa	510
Molluscs		
Tubifex tubifex	Tubificid Worm	0.16
Haliotus sp.	Abalone	30
Nais sp.	Oligochaete	90
Neanthes arenaceodentata	Polychaete Worm	124
Mytilus sp.	Mussel	200
Donax faba	Clam	206
Anadara granosa	Ark Shell	222
Dugesia tigrina	Flatworm	2,450
Amnicola sp.	Spire Snail	2,893
Lamellidens marginalis	Mussel	5,000

3.5.1.2 Terrestrial Organisms

In terrestrial organisms, copper is important in the structure of many enzymes and essential for plant growth, but excess copper can cause cellular membrane instability (Eisler, 1998). In terrestrial plants, there is evidence of toxicity due to copper deficiency, but this does not appear to occur in soil invertebrates (Eisler, 1998). Copper deficiency in birds, such as in the common chicken (*Gallinus domesticus*), can cause sudden death, anemia, and growth impairment (Eisler, 1998). Copper is not accumulated by terrestrial crop plants (Eisler, 1998), but toxicity can include reduced photosynthesis, root damage, DNA damage (Paschke and Redente, 2002), and oxidative stress (Xiong and Wang, 2004). Some effects listed for soil invertebrates include reduced growth, population reduction, and increased mortality (Eisler, 1998). In soil, copper shows toxic effects on plants at concentrations above 60 mg/kg dry weight of soil (Eisler, 1998). There are very few lethal endpoint studies performed on terrestrial organisms, so data from available sources on varying endpoints have been summarized in Table 3-10. Data from the ECOTOX Database (ECOTOX, 2008) for plants were EC25 values for plants grown in soil mix. Avian toxicity values could not be found.

Table 3-10: Toxicity values for terrestrial species

Species	Common Name	End-point	Value	Duration	Response Description	Source
Plants						
Daucus carota	Carrot	PT10	>14 mg/kg	NA	Phytotoxicity threshold	Paschke and Redente, 2002
Manihot esculenta	Cassava	PT10	15 mg/kg	NA	Phytotoxicity threshold	Paschke and Redente, 2002
Brassica oleracea	Cauliflower	PT10	16 mg/kg	NA	Phytotoxicity threshold	Paschke and Redente, 2002
Brassica oleracea	Cabbage	PT10	25 mg/kg	NA	Phytotoxicity threshold	Paschke and Redente, 2002
Spinacia oleracea	Spinach	PT20	25 mg/kg	NA	Phytotoxicity threshold	Paschke and Redente, 2002
Phaseolus vulgaris	Bush Bean	PT10	34 mg/kg	NA	Phytotoxicity threshold	Paschke and Redente, 2002
Zea mays	Corn	PT50	40 mg/kg	NA	Phytotoxicity threshold	Paschke and Redente, 2002
Betula papyrifera	Paper Birch	EC25	59 mg/kg	5-21 d	Reduction in root growth	ECOTOX
Triticum aestivum	Wheat	EC50	77 mg/L	60 d	Reduction in root growth	Paschke and Redente, 2002
Pinus banksiana	Jack Pine	EC25	134 mg/kg	5-21 d	Reduction in root growth	ECOTOX
Pinus strobus	White Pine	EC25	173 mg/kg	5-21 d	Reduction in root growth	ECOTOX
Picea glauca	White Spruce	EC25	183 mg/kg	5-21 d	Reduction in root growth	ECOTOX
Leymus cinereus	Basin Wildrye	EC50	210 mg/L	60 d	Reduction in root growth	Paschke and Redente, 2002
Elymus trachycaulus	Slender Wheatgrass	EC50	220 mg/L	60 d	Reduction in root growth	Paschke and Redente, 2002
Polygonum convolvulus	Bindweed	EC50	291 mg/L	NA	Reduction in root growth	Paschke and Redente, 2002
Poa secunda	Big Bluegrass	EC50	303 mg/L	60 d	Reduction in root growth	Paschke and Redente, 2002
Agrostis gigantea	Redtop	EC50	311 mg/L	60 d	Reduction in root growth	Paschke and Redente, 2002
Deschampsia caespitosa	Tufted Hairgrass	EC50	423 mg/L	60 d	Reduction in root growth	Paschke and Redente, 2002
Pinus resinosa	Norway Pine	EC25	786 mg/kg	5-21 d	Reduction in root growth	ECOTOX
Picea mariana	Black Pine	EC25	4,660 mg/kg	5-21 d	Reduction in root growth	ECOTOX
Invertebrates						
Caenorhabditis elegans	Soil Nematode	LC50	1,061 mg/kg	24 h	Mortality in loam substrate	Eisler, 1998
Lumbricus rubellus	Earthworm	LC50	1,000 mg/kg	6 weeks	Mortality	Eisler, 1998
Eisenia fetida	Earthworm	LC50	555/682 mg/kg	56 d/14 d	Mortality	Eisler, 1998
Colposa steini	Soil Ciliate	EC50	250 µg/L	24 h	Growth reduction	Eisler, 1998

EC = effects concentration; LC = lethal concentration; PT = phytotoxicity threshold

3.5.2 Environmental Risk Assessment

Copper levels in water and soil contaminated by mining operations are at sufficient quantities to be toxic to aquatic and terrestrial organisms near the mining source. Copper is persistent enough to cause long term effects. However, concentrations of copper in soil and water downstream from the source are reduced due to binding and precipitation, and represent much less of a hazard to local organisms.

3.5.3 Environmental Treatment and Remediation

Remediation and mitigation of copper in soil is achieved by amending the soil with materials which copper can bind, causing immobilization (Chaturvedi *et al*., 2007). This can include the addition of organic matter (humic and fulvic acids) and clays to the soil, as well as increasing soil pH to enhance binding with soil functional groups (Chaturvedi *et al*., 2007).

In water, remediation of copper can be achieved by a variety of techniques. The addition of limestone to water to increase pH, causes increased co-precipitation with iron hydroxides (Jordanov *et al.*, 2007; Yun *et al*., 2001). In Jordanov *et al.* (2007) some remediation techniques in water were mentioned; these include using electrochemistry, the addition of organic ligands, and using reactive clay barriers. The addition of chemical chelators to water has also been shown to reduce the aquatic toxicity of copper (Eisler, 1998). Yet, it was mentioned in Jordanov *et al.* (2007) that the most commonly used method, chemical amendment to water, can lead to an increase in sediment and sludge copper concentrations. In Wilson *et al.* (2005), plugging of the channels plagued by acid mine drainage caused decreases in copper concentrations in receiving rivers, but plugging rivers could have far worse impacts for aquatic biota.

3.6 CONCLUSIONS

Most individuals are exposed to copper through their food and water. Found naturally in each, the WHO established copper guidelines of 2 mg/L for drinking water with a maximum tolerable daily intake at 10 mg/L. Copper exposure is most prevalent near mining operations and places that process copper ores or metals but homes with copper piping can also be exposed to higher levels due to leaching from pipes. Proper ventilation is required to minimize the effects of copper fumes on the body, as well as proper hygiene and safety training to minimize exposure to workers in an industrial setting. In the home, allowing the water to run for approximately 30 seconds after prolonged disuse is enough to clear the system of any leached copper. For those individuals with toxic levels of copper exposure, chelating agents such as penicillamine are effective in sequestering the excess. Treatment of symptoms associated with copper poisoning is also recommended. Adding additional organic material and clay to soils with high copper content (like those around smelters) is an effective way of minimizing copper's impact on local flora and fauna. By adding limestone to contaminated waters, the pH is raised and allows copper to precipitate out of solution and settle as sediment.

Copper is an essential metal, not just physiologically where it is a cofactor for multiple enzyme systems, but in socially as well, where it is highly sought after for its conductive properties.

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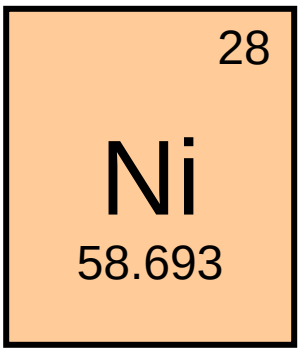
4 NICKEL



4.1 IDENTITY

Symbol: Ni

CAS No.: 7440-02-0

Electron configuration: [Ar] $4s^2$ $3d^8$

4.2 CHARACTERISTICS

4.2.1 Physical and Chemical Properties

Table 4-1: Physical and chemical properties of Nickel

Atomic number	28
Atomic mass	58.69 g/mol
Oxidation states	-1, 0, +2, +3, +4
Isotopes	^{58}Ni- 68.27% ^{60}Ni- 26.10% ^{61}Ni- 1.13% ^{62}Ni- 3.59% ^{64}Ni- 0.91%
Boiling point	3003.0 K
Melting point	1728.0 K
Ionization energies	736.7 kJ/mol
Electron affinity	111.5 kJ/mol
Electronegativity	1.91 (Pauling scale)
Density	8.902 g/cm^3
Physical description	Hard lustrous white metal

Reference: ATSDR, 2005

4.2.1.1 Physical properties

Nickel is a hard, lustrous white metal, which in bulk can resist attack from air and water, making it an excellent protector of rust and oxidation damage. Powdered nickel can spontaneously ignite in air (ATSDR, 2005). It is malleable and can be rolled and flattened. It has ferromagnetic properties and can conduct both heat and electricity with relative ease. It does not occur as free nickel ion in the environment, but is stable as a component of minerals bound to other atoms (ATSDR, 2005).

4.2.1.2 Chemical Properties

Nickel is a transition metal found in group 8 of the periodic table. It has a $4s^2$ $3d^8$ outer electron shell configuration (Sigel and Sigel, 1994). It can exist in -1, 0, +2, +3 +4 oxidation states but Ni^{+2} is the only biologically relevant state (Sigel and Sigel, 1994). Nickel can form alloys with many other metals to increase strength and decrease

corrosion (ASTDR, 2005). Although the process is slow, nickel may often displaces hydrogen from dilute hydrochloric and sulphuric acids. Nickel is highly resistant to corrosion by alkalis, chlorine, fluorine and is somewhat resistant to corrosion by organic acids. Nickel oxide can readily yield salts in the presence of acid. However, a strong oxidizing agent, such as nitric acid, can corrode nickel (ASTDR, 2005).

4.2.2 *Exposure Sources*

Nickel makes up 0.008% of the earths crust (USEPA, 1998). It is listed as the 24th most abundant element and is found in a variety of industrial, natural, and medical settings (USEPA, 1998).

4.2.2.1 Industrial Sources

Nickel is found in batteries, ceramics, metal alloys including stainless steel and coinage metal, electroplating, jewelry, some paints, and colored dyes (USEPA, 1998). Industry workers in fields dealing with spray paint, electricity, and metal work may encounter higher levels. Most exposure is dermal, but ingestion is another route since nickel leaches into groundwater and accumulates in plants that are consumed. Powdered nickel in industrial settings may also be inhaled. Nickel is mined all over the world and high levels of exposure can occurs in workers involved directly in the mining process, refining, smelting, and transport processes (USEPA, 1998).

Releases from industrial sites are presented in the following table.

Table 4-2: Annual releases of nickel into the environment in Canada

Province	**On-site Releases (tonnes)**				**Number of Sites***
	Air	Water	Land	Total	
Saskatchewan	0.119	0	0.076	0.216	5
Quebec	2.055	0.509	0	3.207	33
Ontario	123.649	13.721	0	140.201	221
Nunavut	0	0.001	0	0.001	1
Nova Scotia	3.054	0.031	0	3.184	8
Newfoundland	11	14	0	25	2
New Brunswick	6.402	0.152	0	6.605	6
Manitoba	204.179	19	1.9	225.179	7
British Columbia	0	0	0	0.81	6
Alberta	5.332	1.028	0	6.638	31
Canada (total)	356	49	1.9	412	320

*industrial sites

Reference: NPRI, 2008

4.2.2.2 Natural sources

Nickel can be found naturally in minerals such as garnierite, millerite, niccolite, pentlandite and pyrrhotite (USEPA 1998). Nickel can also be incorporated into many iron and magnesium silicates, sulfates and carbonates, because of its similarity in size to these atoms (USEPA, 1998). While Ni^{2+} is 0.72A, Fe^{2+} is 0.74A and Mg^{2+} is 0.65A.

Nickel is found in vegetables like peas, beans, lentils, lettuce, spinach, cabbage and mushrooms (USEPA, 1998). It can also be found in margarine, some seafoods, and chocolate. Much of the nickel is taken into plants through soil exposure and some plants may hyper-accumulate this element (USEPA, 1998). This element is also often found in wine, beer, and milk because of the small concentrations from their respective ingredients.

4.2.2.3 Medical sources

Another potential route of nickel exposure is through bone implants and replacement joints. Nickel is quite often a major component in the alloys used to makes these implants, because of its strength and resistance to corrosion (ATSDR, 2005). This route of exposure is especially dangerous, and may become life threatening if patients are not screened for nickel allergies. Nickel that comes into direct contact with tissues may elicit damaging inflammatory reactions, and can produce a range of serious complications.

4.2.2.4 Endogenous Sources

Nickel is found in our body in amounts of approximately 10 mg (ASTDR, 2005). The average human has 0.39 mg/kg nickel in the body with 10% of the population containing more than 1.50 mg/kg in their tissues. It is found concentrated in the lungs, the kidneys and in various hormone producing tissues (ATSDR, 2005). In cells, the nickel species and its solubility dictate its cellular distribution. Nickel has a positive charge, and therefore exhibits high affinity for negative charges on various proteins and ion channels. However, the interaction of Nickel with these cellular structures is controversial and will be discussed in subsequent sections. It is thought to play a role in altering membrane properties, influencing the oxidation-reduction system of the cell, and modifying protein interactions leading to altered function (Sigel and Sigel, 1994). In addition, some evidence indicates various hormone levels like prolactin, adrenaline, and aldosterone vary with changes in nickel concentration; however, these mechanisms remain unresolved (Sigel and Sigel, 1994).

4.3 MAMMALIAN HEALTH ASSESSMENT

4.3.1 Toxicokinetics/ toxicodynamics

4.3.1.1 Absorption, distribution, metabolism and excretion

Soluble forms of nickel including nickel chloride and nickel sulphide are passively absorbed in the lungs. Insoluble forms like nickel oxide and nickel ions require specific transporters (USEPA, 1998). Some nickel compounds are phagocytozed by alveolar macrophages in the lungs, but this form of transport is usually reserved for nickel bound to particulate matter. About 35% of inhaled nickel is absorbed into the bloodstream, which is much greater than the bioavailability following oral exposure (USEPA, 1998). The chemical species and the deposition site affect the rate of absorption.

Nickel is poorly absorbed from the gastrointestinal tract. Humans only absorb 0.7% of nickel from food and 17% of the total found in drinking water (Follansbee *et al.*, 1999). Absorption from drinking water was found to be almost 40 times greater than that from food. This indicates that food constituents are able to mediate the bioavailability of zinc. Absorption is theorized to occur through active iron transport pumps in the jejunum and ileum (Follansbee *et al.*, 1999). Nickel generally exhibits poor dermal absorption, but some species such as nickel chloride and nickel sulfate can achieve absorption rates of 77% over a 24 h period (ASTDR, 2005). However, it is generally accepted that nickel absorption through skin is in the range of 0.23% to 3.5% of the applied dose (ASTDR, 2005).

Nickel binds several binding proteins and amino acids in the blood stream, and distributes to most tissues. Most notably serum albumin, L- histidine and the metalloprotein nickeloplasmin are the primary carriers of nickel in the blood (Sigel and Sigel, 1994). In humans, there is very little free nickel in the blood, since most is bound to carrier proteins (Sunderman *et al*., 1992). This metal is able to enter all tissues, but tends to accumulate in the lungs and kidneys. Distribution may be affected if nickel forms complexes with lipids, as these forms are able to cross membranes more easily (Xie *et al.*, 1994). When lipid compounds are added that are able to bind metal ions, there is a significant increase in ion uptake in multiple tissues including the central nervous system and pancreas (Sunderman, 1992). Inert molecules like nickel oxide and lithium nickel oxide tend not to accumulate in nuclear or cytosolic compartments. Conversely, water-soluble salts of nickel accumulate to a greater degree in the cytosol, but to a lesser degree in the nucleus. Slightly soluble compounds like nickel sulphide and nickel chloride produce relatively high concentrations of cytosolic and nuclear nickel (Cicarelli and Wetterhahn, 1982).

Nickel is not destroyed in the body but rather is passed through an extra cellular metabolism process that consists primarily of ligand exchange processes. As stated in the distribution properties section, nickel binds serum albumin, L-histidine, and nickeloplasmin in the blood. There is a proposed model for the transfer of nickel from albumin to the L-histidine molecule regulated by a ternary complex. This L-histidine bound nickel can cross membranes more easily and be excreted. Nickel binds nickeloplasmin at a histidine located at the third position from the amino terminus. The nickel bound to nickeloplasmin is non-exchangeable and cannot be released into the serum. The free nickel ions cannot pass through membranes and may enter the cells only through calcium and sodium transporters. Some nickel complexes are attacked by enzymes upon entering cells. Thus, these enzymes release free nickel from their complexes (ATSDR 2005).

Nickel is primarily excreted in the urine and feces, although all fluids produced and released by the body are potential routes of nickel excretion (Hirano and Suzuki, 1996). Urinary excretion is the primary route of elimination and is an accurate indicator of exposure levels (ASTDR, 2005). Urinary elimination of nickel follows first order kinetics, and the urinary half-life of nickel is approximately 28 h (Hirano and Suzuki, 1996). Renal clearance is between 5.8 and 8.3 mM/min. Chelating agents such as N-benzyl-D-glucaminedithiocarbamate (BGD), diethyldithiocarbamate (DDTC) and di-

hydroxyethyldithiocarbamate (DHED) were found to increase nickel excretion in feces and urine. In addition, these chelating agents were effective in immobilizing nickel and lowering systemic levels (Xie *et al.,* 1994).

4.3.1.2 Cellular interactions

4.3.1.2.1 Nickel binding proteins

It is difficult to ascertain exactly what the functional role of nickel is in the body. There have been nutritional studies that suggest nickel is a necessary trace element for biological processes. The presence of a nickel specific carrier in the blood lends credibility to this argument (Sigel and Sigel, 1994). However, it is still controversial whether or not nickel is an essential micronutrient. Even though iron and copper possess the same valencies in vivo, it is unclear whether or not their functionality would be compromised following substitution with nickel. Furthermore, when considering at the proteins that bind nickel, another debate surrounds whether the protein binds nickel simply because it recognizes the presence of the ion, like a protein carrier, or if the nickel conveys some sort of functionality to the protein, acting as a prosthetic group as is seen in metalloenzymes (Sigel and Sigel, 1994). Nickel can also alter the function of proteins that do not have a native nickel ion as a part of their structure through ionic interactions with charged amino acids side chains, and the alteration of salt bridges and protein interactions. Some of the known nickel binding proteins are described below.

4.3.1.2.2 Serum albumin

In humans, this protein contains binding sites where divalent cations like nickel can bind reversibly. This binding site contains a histidine molecule, which can bind the nickel ion. Molecular differences in members of a species can determine how much nickel can bind to this protein. It has been found that between 90 and 93% of nickel in the blood is bound to albumin, making it the primary serum carrier of this element (Sigel and Sigel, 1994).

4.3.1.2.3 Nickeloplasmin

Nickeloplasmin is a plasma nickel binding protein found in human and rabbit serum. It belongs to the family of alpha macroglobulins and is the only protein found so far in humans that shows specificity for nickel ions. It binds nickel tightly and does not allow release and migration. This aids in detoxification but slows elimination (Sigel and Sigel, 1994).

4.3.1.2.4 Lectins

This family of proteins binds sugar monomers like D-mannose and D-glucose and plays a role in bacterial recognition and attachment to host cells during infection, and soluble glycoprotein binding in animals. These proteins normally contain one Mn^{2+} or Ca^{2+} ion in the active site of the native protein that gives the enzyme its functionality. However,

these ions can be readily substituted with other divalent cations including, under certain circumstances, nickel. Many of these substituted forms are as active as the original enzyme complex (Sigel and Sigel, 1994).

4.3.1.2.5 Hemoproteins

Nickel can be incorporated into the porphyrin ring system of heme in both hemoglobin and myoglobin in place of the normal Fe^{2+}. It binds to the coordinate bonds in much the same way as iron, but incorporates the imidazole side chain of the axial histidine as the 5th ligand. If nickel replaces the resident iron, the protein can no longer bind oxygen and its functionality is lost. In this situation, substitution of the native iron for nickel eliminates the functionality (Sigel and Sigel, 1994).

4.3.1.2.6 G-Actin

In some mammals, the presence of divalent ions in cells (including nickel) has been shown to increase the binding affinity of ATP for the globular actin protein (Sigel and Sigel, 1994). It has been suggested that the divalent ion binds to two terminal phosphate residues in the ATP. This means that the ATP- bound actin will form microfilaments at a much faster rate (Sigel and Sigel, 1994). This may increase cellular contractions or cell movement. This is a case where nickel does not act directly on the protein itself, but participates in a change of function, for this protein it is an up-regulation event.

4.3.1.2.7 Enzyme interactions

Many enzymes contain metal ions as part of the enzyme complex, or as a side binding agent like a prosthetic group or a cofactor. The proteins mentioned below are enzymes whose functions are altered when they encounter a nickel ion. *In vitro* studies have shown that nickel can alter the enzymatic processes of several proteins, most notably, the inhibition of the brain ATPase and myocardium phosphatase (Sigel and Sigel, 1994). Nickel has also been shown to activate the enzyme allantoicase, an enzyme that acts in the urea pathway, after replacement of the native Mg^{2+} with Ni^{2+} (Sigel and Sigel, 1994).

4.3.1.2.8 Azurin

This 14 kDa protein is a blue copper protein that is part of the oxioreductase family of enzymes (Sigel *et al*., 1994). Azurin catalyzes the reaction that reduces arsenate to arsenite and is important in the storage and detoxification of arsenic in many species (Sigel and Sigel, 1994). In its normal form, azurin has a Cu^{2+} ion in the active site. If this Cu^{2+} ion is removed, the apoprotein can sequester nickel at this site (Sigel and Sigel, 1994).

4.3.1.2.9 Metallothionein

Nickel-metallothionein ion complexes are very stable and it is thought that one of the roles of these proteins is to sequester nickel, and prevent toxicity (Sigel and Sigel, 1994).

4.3.2 Toxicity and toxicological data

4.3.2.1 Endocrine toxicity

No current data exist for human exposure. No significant effects have been observed in animal studies.

4.3.2.2 Reproductive and developmental toxicity

A number of studies have examined the reproductive effects of nickel following oral exposure to rats, mice, or dogs. Pandey *et al.* (1999) reported a significant accumulation of nickel in the epididymis, testes, seminal vesicles, and prostate gland in mice orally exposed to nickel sulfate for 35 d. The accumulation of nickel in male reproductive tissues correlated with an observed increase in histological damage in the epididymis and seminal vesicles. Regressed epithelium and vacuolated cells were observed in the epididymis of mice administered 1.1 mg Ni/kg BW as nickel sulfate through gavage 5 d/week for 35 d (Pandey *et al*. 1999). In the seminiferous tubules, atrophy of centrally located tubules and altered spermatogenesis was observed in mice administered 1.1 mg Ni/kg BW as nickel sulphate administered by gavage 5 d per week over a duration of 35 weeks (Pandey, 1999). Käkelä *et al*. (1999) reported a statistically significant decrease in seminiferous tubule diameter in rats exposed to 3.6 mg Ni/kg BW/d as nickel chloride in drinking water for 28 or 42 d. A significant decrease in basal spermatogonia was also observed in the rats exposed for 28 d, but was not seen in the rats exposed for 42 d. However, in this study, the body weights of males exposed for 28 d appear to be lower than control body weights which may have been the cause of the findings. Other studies have not found structural alterations in male or female reproductive tissues in rats administered up to 25 mg Ni/kg/d as nickel chloride for 91 d (American Biogenic Corp., 1988). Mice administered ≥2.2 mg Ni/kg as nickel sulfate showed a significant decreases in sperm count, sperm motility and some sperm abnormalities including detached head, missing or curved neck, and curved, bent, rounded, looped, and folded tail. (Pandey and Srivastava 2000). However, there were no effects were observed at 1.1 or 1.2 mg Ni/kg BW as nickel sulfate or nickel chloride, respectively. Similarly, Pandey *et al.* (1999) reported decreases in sperm count and motility in mice that were administered 2.2 mg Ni/kg BW as nickel sulfate, 5 d/week for 35 d.

Male-only exposure or male and female exposure to 3.6 mg Ni/kg/d as nickel chloride in drinking water resulted in decreased fertility in rats exposed for 28 d prior to mating (Käkelä *et al.*, 1999). Male rats exposed to 3.6 mg Ni/kg/d for 42 d prior to mating with unexposed females experienced a small decrease in fertility (83 versus 100%) (Käkelä *et al.,* 1999). This result suggests possible regeneration of reproductive tissues in the exposed males.

A complete list of observed changes from various studies is given below.

Table 4-3: Reproductive toxicity of different forms of nickel through varying routes of exposure.

Route of exposure	Com-pound	Species	Duration of exposure	NOAEL	LOAEL	Reference
Inhalation	Nickel sulfate	Fischer-344 rat	2 years 5 d/ week, 6 h/d	0.11 mg/m^3		NTP, 1996c
Inhalation	Nickel sulfate	B6C3F1 mouse	2 years, 5 d/ week, 6 h/d	0.22 mg/m^3		NTP, 1996c
Inhalation	Nickel sulfate	Fischer-344 rat	13 weeks, 5 d/ week, 6 h/d	0.44 mg/m^3		NTP, 1996c
Inhalation	Nickel sulfate	B6C3F1 mouse	13 weeks. 5 d/ week 6 h/d	0.44 mg/m^3		NTP, 1996c
Inhalation	Nickel sub-sulfide	B6C3F1 Mouse	2 years, 5 d/ week, 6 h/d	0.73 mg/m^3		NTP, 1996b
Inhalation	Nickel sub-sulfide	B6C3F1 Mouse	2 years, 5 d/ week, 6 h/d	0.88 mg/m^3		NTP, 1996b
Inhalation	Nickel sulfate	B6C3F1 mouse	12 d in 16 d period, 6 h/d	1.4 mg/m^3		NTP, 1996c
Inhalation	Nickel sub-sulfide	Fischer-344 rat	13 weeks, 5 d/ week, 6 h/d	1.83 mg/m^3		NTP, 1996b
Inhalation	Nickel sub-sulfide	B6C3F1 Mouse	13 weeks, 5 d/ week, 6 h/d	1.83 mg/m^3		NTP, 1996b
Inhalation	Nickel oxide	Fischer-344 rat (male)	2 years, 5 d/ week, 6 h/d	2 mg/m^3		NTP, 1996a
Inhalation	Nickel sub-sulfide	B6C3F1 Mouse	12 d in 16 d period, 6 h/d	3.65 mg/m^3		NTP, 1996b
Inhalation	Nickel oxide	Fischer-344 rat (male)	13 weeks, 5 d/ week 6 h/d	3.9 mg/m^3	7.9 mg/m^3 (decreased sperm concentration)	NTP, 1996a
Inhalation	Nickel oxide	B6C3F1 Mouse	2 yr 5d/wk 6hr/d	3.9 mg/m^3		NTP, 1996a
Inhalation	Nickel sub-sulfide	Fischer-344 rat	12 d in 16 d period, 6 h/d	7.33 mg/m^3		NTP, 1996b
Inhalation	Nickel oxide	B6C3F1 Mouse	13 weeks, 5 d/ week, 6 h/d	7.9 mg/m^3		NTP, 1996a

Route of exposure	Com-pound	Species	Duration of exposure	NOAEL	LOAEL	Reference
Inhalation	Nickel sulfate	Fischer-344 rat	12 d in 16 d period, 6 h/d	12.2 mg/m^3		NTP, 1996c
Inhalation	Nickel oxide	Fischer-344 rat (male)	12 d in 16 d period, 6 h/d	23.6 mg/m^3		NTP, 1996a
Inhalation	Nickel oxide	B6C3F1 Mouse	12 d in 16 d period, 6 h/d	23.6 mg/m^3		NTP, 1996a
Oral	Nickel sulfate	Wistar rat (female)	about 24 weeks	90 mg/kg BW/d		Ambrose *et al.*, 1976
Oral	Nickel sulfate	Sprague-Dawley rat (male)	daily for 13 weeks (W)	28.8 mg/kg BW /d		Obone *et al.*, 1999
Oral	Nickel sulfate	Sprague-Dawley rat (male)	daily, 18 weeks (GW)	2.2 mg/kg BW /d		Spring-born Lab-oratories, 2000a
Oral	Nickel sulfate	Sprague-Dawley rat (male)	daily, 35-56 d (GW)	16.7 mg/kg BW/d		Spring-born Laboratories, 2000a
Oral	Nickel sulfate	NS mouse (male)	35 d, 5 d/ week, (GW)	1.1 mg/kg BW/d	2.2 mg/kg BW/ d (decreased sperm motility; increased sperm abnormalities)	Pandey and Srivastava, 2000
Oral	Nickel sulfate	Swiss mouse (male)	35 d, 5 d/week (GW)		1.1 mg/kg BW/d (increased total number of sperm abnormalities)	Pandey *et al*., 1999
Oral	Nickel chloride				2.2 mg/kg BW/ d (decreased fertility)	Pandey *et al.*, 1999
Oral	Nickel chloride	Wistar rat (female)	daily, 62 d (W)	13 mg/kg BW/d		Kakela *et al.*, 1999
Oral	Nickel chloride	Wistar rat (male)	daily 28 or 42 d (W)		3.6 mg/kg BW/ d (decreased fertility)	Kakela *et al.*, 1999
Oral	Nickel chloride	Wistar rat	daily 28-76 d (W)		3.6 mg/kg BW/ d (decreased fertility)	Kakela *et al.*, 1999
Oral	Nickel chloride	CD rat	27-30 weeks (W) 21-24 weeks (W)	7 mg/kg BW/ d	30 mg/kg BW/ d (increased gestation length in first P0 pregnancy)	RTI, 1988a, 1988b
Oral	Nickel	Long-Evans	11 wk	31.6 mg/kg		Smith *et al.*

Route of exposure	Com-pound	Species	Duration of exposure	NOAEL	LOAEL	Reference
	chloride	rat	Breeding lactation 2 litters (W)	BW/ d		1993
Oral	Nickel chloride	NS mouse (male)	35 d, 5 d/week	1.2 mg/kg BW/ d	2.5 mg/kg BW/ d (decreased sperm motility and count; increased sperm abnormalities)	Pandey and Srivastava 2000
Oral	Nickel nitrate	Lacca mouse (male)	Once (GW)		23 mg/kg BW/ d (3.7-fold increase in sperm head abnormalities)	Sobti and Gill 1989
Dermal	Nickel sulfate	Rat (male)	daily for 30 d	40 mg/kg BW/ d	60 mg/kg BW/ d (degeneration and edema of seminiferous tubules)	Mathur *et al.*, 1977

GW = gavage in water, W = drinking water

Table 4-4: Developmental toxicity data for nickel

Route of Exposure	Compound	Species	Duration of exposure	NOAEL	LOAEL	Reference
Inhalation	Nickel oxide	Wistar rat	Gd 1-21 23.6 hr/d	0.8 mg/m^3	1.6 mg/m^3 (decreased fetal body weights)	Weischer *et al.* 1980
Oral	Nickel sulfate	Wistar rat	about 24 wk [F]		22.5 mg/kg BW/d (increased number of stillborns)	Ambrose *et al.*, 1976
Oral	Nickel chloride	Wistar rat (male)	daily 28 or 42 d (W)		3.6 mg/kg BW/d (decreased pup viability and survival)	Kakela *et al.*, 1999
Oral	Nickel chloride	Wistar rat	daily 28--76 d (W)		3.6 mg/kg BW/d (increased fetal mortality and decreased pup survival)	Kakela *et al.*, 1999
Oral	Nickel chloride	Long-Evans rat	11 wk Breeding lactation 2 litters (W)		1.3 mg/kg BW/d (decreased pup survival)	Smith *et al.*, 1993
Oral	Nickel sulfate	Sprague-	daily	2.2 mg/kg		Spring-born

Route of Exposure	Compound	Species	Duration of exposure	NOAEL	LOAEL	Reference
		Dawley rat	18 weeks (GW)	BW/d		Laboratories 2000a
Oral	Nickel chloride	Wistar rat (female)	daily 62 d (W)	4 mg/kg BW/d	13 mg/kg BW/d (decreased litter size and pup survival)	Kakela *et al.*, 1999
Oral	Nickel sulfate	Sprague-Dawley rat (female)	daily 49-70 d (GW)	4.5 mg/kg BW/d	6.7 mg/kg BW/d (increased post-implantation loss)	Springborn Laboratories, 2000b
Oral	Nickel chloride	CD rat (male)	F: 27-30 weeks M: 21-24 weeks (W)	7 mg/kg BW/d	30 mg/kg BW/d (increased mortality in F1b rats on pnd 22-42; decreased pup body weight in F1b rats)	RTI, 1988a, 1988b
Oral	Nickel chloride	CD-1 rat	Gd 8-12 1x/d (G)	45.3 mg/kg BW/d		Gray *et al.* 1986
Oral	Nickel chloride	CD-1 rat	Gd 2-17 (W)	80 mg/kg BW/d	160 mg/kg BW/d (increased spontaneous abortions)	Berman and Rehnberg, 1983
Oral	Nickel chloride	Mice	Gd 8-12 (GW)	90.6 mg/kg BW/d		Seiden-berg *et al.*, 1986

Gd = gestational d , GW = gavage in water, [F] = feed, W = drinking water, G = Gavage

4.3.2.3 Immunotoxicity

The following chart contains the available animal studies on the immunotoxic endpoints of nickel.

Table 4-5: Immunotoxicity of different forms of nickel through varying routes of exposure.

Route of Exposure	Compound	Species	Exposure	NOAEL	LOAEL	Reference
Inhalation	Nickel oxide	Fishcher-344 rat	2 years, 5 d/ week, 6 h/d		0.5 mg/m^3 (M) (lymphoid hyperplasia in bronchial lymph node)	NTP, 1996a
Inhalation	Nickel oxide	Wistar rat (male)	4 weeks, 5 d/ week,		9.2 mg/m^3 (increased	Morimoto *et al.*, 1995

Route of Exposure	Compound	Species	Exposure	NOAEL	LOAEL	Reference
			8 h/d		production of tumor necrosis factor by alveolar macrophages)	
Inhalation	Nickel oxide	B6C3F1 mouse (female)	65 d, 5 d/ week, 6 h/d		0.47 mg/m^3 (decreased alveolar macrophage activity)	Haley *et al.*, 1990
Inhalation	Nickel oxide	B6C3F1 Mouse	2 years, 5 d/ week, 6 h/d		1 mg/m^3 (bronchial lymph node hyperplasia)	NTP, 1996a
Inhalation	Nickel subsulfide	Fishcher-344 rat	2 years, 5 d/ week, 6 h/d		0.11 mg/m^3 (lymphoid hyperplasia in bronchial lymph nodes)	NTP, 1996b
Inhalation	Nickel subsulfide	B6C3F1 mouse	2 years, 5 d/ week, 6 h/d		0.44 mg/m^3 (lymphoid hyperplasia in bronchial lymph nodes)	NTP, 1996b
Inhalation	Nickel sulfate	CD-1 mouse (female)	2 h		0.455 mg/m^3 (increased susceptibility to Streptococcal infection)	Adkins *et al.*, 1979
Inhalation	Nickel chloride	NS rabbit (male)	4-6 weeks, 5 d/week, 6 h/d		0.6 mg/m^3 (decrease lysozyme activity in alveolar macrophages)	Johansson *et al.*, 1987
Inhalation	Nickel chloride	NS rabbit (male)	4 months, 5 d/week, 6 h/d		0.6 mg/m^3 (decreased macrophage lysosomal activity)	Johansson *et al.*, 1988a, 1989
Inhalation	Nickel chloride	CD-1 mouse (female)	2 h		0.657 mg/m^3 (decreased ability to clear bacteria from lungs)	Adkins *et al.*, 1979
Inhalation	Metallic nickel	NS rabbit (male)	3 or 6 months, 5 d/week, 6 h/d		1 mg/m^3 (inactive macrophage surfaces)	Johansson *et al.*, 1980
Inhalation	Nickel oxide	Wistar rat	4 months	0.025 mg/m^3	0.15 mg/m^3 (impaired humoral	Spiegelberg *et al.*, 1984

Route of Exposure	Compound	Species	Exposure	NOAEL	LOAEL	Reference
					immunity)	
Inhalation	Nickel sulfate	Fishcher-344 rat	2 years, 5 d/ week 6 h/d	0.06 mg/m^3	0.11 mg/m^3 (lymphoid hyperplasia in bronchial lymph nodes)	NTP, 1996c
Inhalation	Nickel chloride	Swiss mouse (female)	2 h	0.1 mg/m^3	0.25 mg/m^3 (impaired humoral immunity)	Graham *et al.,* 1978
Inhalation	Nickel subsulfide	Fishcher-344 rat	13 weeks, 5 d/ week 6 h/d	0.11 mg/m^3	0.22 mg/m^3 (lymphoid hyperplasia in bronchial lymph nodes)	NTP, 1996b
Inhalation	Nickel subsulfide	B6C3F1 mouse (female)	65 d 5 d/ week 6 h/d	0.11 mg/m^3	0.45 mg/m^3 (decreased alveolar macrophage phagocytic activity)	Haley *et al.,* 1990
Inhalation	Nickel sulfate	Fishcher-344 rat	13 weeks, 5 d/ week, 6 h/d	0.11 mg/m^3	0.22 mg/m^3 (lymphoid hyperplasia in bronchial and mediastinal lymph nodes)	NTP, 1996c
Inhalation	Nickel oxide	Wistar rat	4 weeks	0.1 mg/m^3	0.2 mg/m^3 (impaired humoral immunity)	Spiegelberg *et al.,* 1984
Inhalation	Nickel sulfate	B6C3F1 mouse	2 years,5 d/ week,6 h/d	0.11 mg/m^3	0.22 mg/m^3 (bronchial lymph node hyperplasia)	NTP, 1996c
Inhalation	Nickel sulfate	B6C3F1 mouse (female)	65 d,5 d/ week,6 h/d	0.11 mg/m^3	0.45 mg/m^3 (decreased resistance to tumor challenge)	Haley *et al.,* 1990
Inhalation	Nickel chloride	CD-1 mouse (female)	2 h	0.369 mg/m^3	0.499 mg/m^3 (increased susceptibility to Streptococcal infection)	Adkins *et al.,* 1979
Inhalation	Nickel subsulfide	B6C3F1 mouse	12 d in 16 d period, 6 h/d	0.44 mg/m^3	0.88 mg/m^3 (lymphoid hyperplasia in bronchial lymph nodes)	NTP, 1996b
Inhalation	Nickel subsulfide	B6C3F1 mouse	13 weeks, 5 d/ week,	0.44 mg/m^3	0.88 mg/m^3 (lymphoid	NTP, 1996b

Route of Exposure	Compound	Species	Exposure	NOAEL	LOAEL	Reference
		(female)	6 h/d		hyperplasia in bronchial lymph nodes)	
Inhalation	Nickel sulfate	B6C3F1 mouse (female)	13 weeks,5 d/ week,6 h/d	0.22 mg/m^3	0.44 mg/m^3 (hyperplasia of bronchial lymph nodes)	NTP, 1996c
Inhalation	Nickel sulfate	Fischer-344 mouse (female)	12 d in 16 d period, 6 h/d	0.7 mg/m^3	1.4 mg/m^3 (hyperplasia in bronchial and mediastinal lymph nodes)	NTP, 1996c
Inhalation	Nickel oxide	Fishcher-344 rat	13 weeks, 5 d/ week, 6 h/d	0.9 mg/m^3	2 mg/m^3 (lymphoid hyperplasia in bronchial lymph nodes)	NTP, 1996a
Inhalation	Nickel oxide	B6C3F1 Mouse	13 weeks, 5 d/ week, 6 h/d	0.9 mg/m^3	2 mg/m^3 (lymphoid hyperplasia in bronchial lymph nodes)	NTP, 1996a
Inhalation	Nickel sulfate	B6C3F1 mouse	12 d in 16 d period, 6 h/d	3.1 mg/m^3		NTP, 1996c
Inhalation	Nickel sulfate	Sprague-Dawley rat (male)	daily for 13 weeks	5.75 mg/m^3	14.4 mg/m^3 (alterations in spleen and thymus lymphocyte T-cell and B-cell sub-populations)	Obone *et al.,* 1999
Inhalation	Nickel subsulfide	Fishcher-344 rat	12 d in 16 d period, 6 h/d	7.33 mg/m^3		NTP, 1996b
Inhalation	Nickel oxide	Fishcher-344 rat	12 d in 16 d period, 6 h/d	23.6 mg/m^3		NTP, 1996a
Inhalation	Nickel oxide	B6C3F mouse1	12 d in 16 d period,6 h/d	23.6 mg/m^3		NTP, 1996a
Inhalation	Nickel sulfate	Wistar rat (female)	2 years	187.5 mg/m^3		Ambrose *et al.,* 1976

Route of Exposure	Compound	Species	Exposure	NOAEL	LOAEL	Reference
Oral	Nickel sulfate	B6C3F1 Mouse (female)	180 d (W)		44 mg/ kg BW/ d (mild thymic atrophy, impaired B-cell immune function, decreased granulocyte macrophage progenitor cell levels)	Dieter *et al.*, 1988
Oral	Nickel chloride	BALB/c mouse	10-11weeks (W)		20.3 mg/ kg BW/ d (F) (enhanced inflammatory response in the hearts of mice challenged with coxsackie virus B3)	Ilback *et al.*, 1994
Dermal	Nickel sulfate	Mouse (C3H:Hej) (female)	once occluded for 7 d		1 % (development of dermal sensitization)	Siller and Seymour, 1994
Oral	Nickel sulfate	Dog (Beagle) (female)	2 years	62.5 mg/ kg BW/ d		Ambrose *et al.*, 1976

W = drinking water

4.3.2.4 Neurotoxicity

Chronic toxicity tests have shown no significant neurological effects following nickel exposure. However, acute and sub-chronic studies demonstrated neurological abnormalities. These studies are presented in Table 4-6.

Table 4-6: Neurotoxicity of Nickel

Route of Exposure	Compound	Species	Exposure	NOAEL	LOAEL	Reference
Inhalation	Nickel sulfate	Long-Evans rat (male)	4, 8, 12, 16 d, 6 h/d		0.635 mg/m^3 (decrease in number of bipolar receptor cells in nasal olfactory epithelium)	Evans *et al.*, 1995

Route of Exposure	Compound	Species	Exposure	NOAEL	LOAEL	Reference
Oral	Nickel chloride	Sprague-Dawley rat	91 d (GW)	1.2 mg/kg BW/ d	8.6 mg/kg BW/ d (ataxia, prostration, hypothermia)	American Biogenics Corp., 1988
Oral	Nickel sulfate	Dog (Beagle)	2 years	62.5 mg/kg BW/ d		Ambrose *et al.*, 1976
Oral	Nickel sulfate	Wistar rat	2 years	187.5 mg/kg BW/ d		Ambrose *et al.*, 1976

GW = gavage in water

4.3.2.5 Genotoxicity

There is little evidence of adduct formation from nickel, thus the genetic effects of Ni (II) are largely dependent on redox reactions between Ni(II) and amino acids and chromatin proteins, but not DNA (Kasprzak *et al.*, 2003). This is because Ni(II) has a much higher binding capacity to cellular proteins than DNA. Its interactions with protein molecules produce conformational changes and functional disruption of the protein's structure. The consequence of this is inhibition of DNA repair enzymes. Table 4-7 displays *in vivo* study results for the genotoxicity of nickel while Table 4-8 displays *in vitro* results.

Table 4-7: Genotoxicity of Nickel *in Vivo*

Species	Compound	End point	Results	Reference
D. melanogaster	Nickel nitrate or chloride	Gene mutation	-	Rasmuson 1985
D. melanogaster	Nickel sulfate	Recessive lethal	+	Rodriguez-Arnaiz and Ramos 1986
D. melanogaster	Nickel chloride	Gene mutation (wing spot test)	- /+	Ogawa *et al.*, 1994
Human lymphocytes	Nickel oxide, nickel subsulfide	Chromosome gaps	+	Waksvik and Boysen 1982
Human lymphocytes	Nickel oxide, nickel subsulfide	Sister chromatid exchange	-	Waksvik and Boysen 1982
Rat bone marrow and spermatogonial cells	Nickel sulfate	Chromosome aberrations	-	Mathur *et al.*, 1978
Mouse bone marrow cells	Nickel chloride (intraperitoneal)	Chromosome aberrations	+	Dhir *et al.*, 1991
Mouse bone marrow cells	Nickel chloride, nickel sulfate, nickel oxide (intraperitoneal)	Micronucleus test	-	Morita *et al.*, 1997
Rat bone marrow cells	Nickel sulfate (oral)	Micronucleus test	-	Covance Laboratories, Inc.
Mouse bone marrow cells	Nickel chloride (intraperitoneal)	Micronucleus test	-	Deknudt and Leonard 1982
Mouse lung, mouse nasal	Nickel subsulfide	Gene mutation	-	Mayer *et al.*, 1998

mucosa, rat lung, rat nasal mucosa		(inhalation)		
Mouse	Nickel acetate (intraperitoneal)	Dominant lethal	-	Deknudt and Leonard 1982

Table 4-8: Genotoxicity of Nickel *in Vitro*

Species	Compound	End point	Results	Reference
Salmonella typhimurium	Nickel chloride, nickel nitrate, nickel sulfate	Gene mutation Frequency	-	Arlauskas *et al.*, 1985; Biggart and Costa 1986; Marzin and Phi 1985; Wong 1988
Escherichia coli WP2	Nickel chloride	Gene mutation Frequency	-	Green *et al.*, 1976
Cornebacterium sp.	Nickel chloride	Gene mutation Frequency	+	Pikalek and Necasek, 1983
E. coli	Nickel chloride	DNA replication rate	+	Chin *et al.*, 1994
Bacillus subtilis	Nickel oxide and trioxide	DNA damage (rec assay)	-	Kanematsu *et al.*, 1980
Saccharomyces cerevesiae	Nickel sulfate	Reverse mutation	-	Singh 1984
CHO cells	Nickel chloride	Gene mutation at HGPRT locus	-	Hsie *et al.*, 1979
Virus-infected mouse sarcoma cells	Nickel chloride	Induction of revertant Foci	+	Biggart and Murphy 1988; Biggart *et al.* 1987
Mouse lymphoma cells	Nickel chloride, nickel sulfate	Forward mutation	+	Amacher and Paillet 1980; McGregor *et al.*, 1988
Chinese hamster V79 cells	Nickel chloride	Gene mutation at HGPRT locus	+	Hartwig and Beyersmann 1989; Miyaki *et al.*, 1979
Chinese hamster ovary AS52 cells	Nickel oxide (black and green); amorphous nickel sulfide; nickel subsulfide nickel chloride; nickel sulfate; nickel acetate	Gene mutation at *grp* locus	+	Fletcher *et al.* 1994
CD2F1 mouse lung and nasal mucosa cells	Nickel subsulfide	DNA fragmentation	+	Mayer *et al.*, 1998
Chinese hamster ovary	Crystalline NiS,	DNA protein	+	Hamilton-Koch *et*

Species	Compound	End point	Results	Reference
cells	nickel chloride	crosslinks/single strand breaks		*al.*, 1986; Patierno and Costa, 1985
Human diploid fibroblasts	Nickel chloride	DNA single strand Breaks	-	Hamiltion-Koch *et al.*,1986
Human gastric mucosal cells	Nickel sulfate	DNA damage (comet analysis)	-	Pool-Zobel *et al.*, 1994
Human HeLa cells	Nickel chloride	DNA replication	+	Chin et al. 1994
Hamster cells	Nickel sulfate, nickel chloride; crystalline NiS	Sister chromatid Exchange	+	Andersen 1983; Larramendy *et al.*, 1981; Ohno *et al.*, 1982; Saxholm et al. 1981
Human lymphocytes	Nickel sulfate, nickel sulfide	Sister chromatid Exchange	+	Andersen 1983; Larramendy *et al.*, 1981; Saxholm *et al.*, 1981; Wulf 1980
Hamster cells	Nickel sulfate, nickel chloride nickel mono-sulfide	Chromosome Aberration	+	Conway and Costa 1989; Larramendy *et al.*, 1981; Sen and Costa 1986b; Sen *et al.*, 1987
Human lymphocytes	Nickel sulfate	Chromosome Aberration	+	Larramendy *et al.*, 1981
Human lymphocytes	Nickel subsulfide	Sister chromatid Exchange	+	Arrouijal *et al.*, 1991
Human lymphocytes	Nickel subsulfide	Metaphase analysis	+	Arrouijal *et al.*, 1991
Human lymphocytes	Nickel subsulfide	Micronucleus Formation	+	Arrouijal *et al.*, 1991
Human bronchial epithelial cells	Nickel sulfate	Chromosome aberration	+	Lechner *et al.*, 1984
Hamster cell and C3H/10T1/2 cells	Nickel monosulfide, nickel subsulfide, nickel chloride, nickel, nickel oxide or trioxide	Cell transformation	+	Conway and Costa 1989; Costa and Heck 1982; Costa and Mollenhauer 1980; Costa *et al.*, 1982; DiPaolo and Casto 1979; Hansen and Stern 1984; Saxholm *et al.*, 1981
Mouse embryo fibroblasts	Nickel sulfate, nickel chloride	Cell transformation	-	Miura *et al.*, 1989
Mouse embryo fibroblasts	Nickel subsulfide, nickel monosulfide,	Cell transformation	+	Miura *et al.*, 1989

Species	Compound	End point	Results	Reference
	nickel oxide			
Human foreskin cells	Nickel subsulfide, nickel oxide, nickel sulfate, nickel acetate	Cell transformation	+	Biedermann and Landolph 1987

4.3.2.6 Carcinogenicity

Carcinogenesis associated with nickel has not been well studied. Epidemiologic studies have demonstrated increased mortality from carcinomas of the lung and nasal cavities in nickel refinery workers chronically exposed to inhalation of nickel-containing dusts and fumes from roasting, smelting, and electrolysis processes. The respiratory tract cancers in nickel refinery workers have been associated with inhalation exposures to nickel compounds with low aqueous solubility such as Ni3S2, NiO; as well as soluble nickel compounds like NiSO4. Some studies have demonstrated that the risk for cancer of the respiratory tract is increased when the atmospheric concentration of soluble nickel exceeds 1 mg Ni/m3 and insoluble derivatives exceeds 10 mg Ni/m3. Nickel accumulates in the nasal mucosa of exposed workers, and its concentration is proportional to the length of exposure. Since its biologic half-life is 3½ years, its concentration remains high even after cessation of exposure. The following charts summarize the available animal and human studies.

Table 4-9: Carcinogenicity of nickel

Route of Exposure	Species	Chemical Form	Exposure	LOAEL	Reference
Inhalation	Fischer-344 rat	Nickel subsulfide	78 weeks, 5 d/week 6 h/d	0.7 mg/m^3 (CEL: lung adenomas, adenocarcinomas, squamous cell carcinoma, 14% treated, 1% controls)	Ottolenghi *et al.*, 1974
Inhalation	Fischer-344 rat	Nickel subsulfide	2 years 6 h/d 5 d/week	0.73 mg/m^3 (CEL: alveolar/bronchiolar adenoma or carcinoma)	NTP, 1996b
Inhalation	Human	Soluble	Occupational	1 mg/m^3 (CEL: lung and nasal cancers)	ICNCM, 1990
Inhalation	Fischer-344 rat (male)	Nickel oxide	2 years 5 d/week 6 h/d	1 mg/m^3 (CEL: alveolar/bronchiolar adenoma or carcinoma)	NTP, 1996a
Inhalation	Human	Combination of soluble and less soluble forms	Occupational	10 mg/m^3 (CEL: lung and nasal cancers)	ICNCM, 1990

CEL = cancer effect level

4.3.3.1 Renal toxicity

Animal studies have demonstrated nephrotoxicity following exposure to nickel and nickel compounds. Furthermore, it has been shown that nickel inhibits normal renal function by altering the reuptake of ions in the renal tubules. Nickel binds transporters found in the membrane lining the tubules. Once bound, it inhibits reabsorption of other ions and proteins. In addition, nickel is also able to form reactive oxygen species, which contributes to membrane damage (Pereira *et al.*, 1997). In other *in vivo* studies, animals exposed to nickel experienced reduced glomerular function (Templeton, 1987).

Nickel and other heavy metals have also shown to cause stress on the endoplasmic reticulum of renal cells (Hiramatsua, 2007). Endoplasmic reticulum (ER) stress-responsive alkaline phosphatase (ES-TRAP) serves as a sensitive indicator for ER stress. Nickel acts by reducing ES-TRAP activity and then indirectly inducing the expression of glucose regulating protein 78 (GRP 78) (Hiramatsua, 2007). GRP78 is a key regulator of endoplasmic reticulum (ER) homeostasis (Luo *et al.*, 2006). It does this because it has multiple roles in protein folding, ER calcium binding, and controlling of the activation of transmembrane ER stress sensors (Luo *et al.*, 2006). Therefore, nickel may induce stress on renal cell endoplasmic reticulum by increasing expression of GRP78 and altering ER homeostasis.

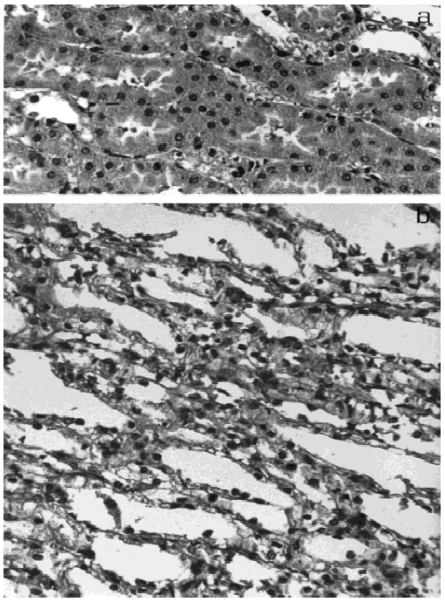


Figure 4-1: Histological section of mouse kidney at the end of a four week study. Top: Normal epithelium of a control mouse given control injection of Hank's Balanced Salt Solution. Bottom: Discontinuous epithelium from a mouse after the fourth week of receiving 300 mg/kg BW/d nickel injection. (Pereira, 1997)

4.3.3.3 Hepatic toxicity

Nickel induced hepatotoxicity is evident by swollen and clear cytoplasm of hepatocytes. This is an indicator of compromised function (Pereira *et al.*, 1997). In some instances, nickel may cross the hepatocellular membrane in which it would become sequestered in lysosomes. Within lysosomes, nickel may form reactive oxygen species (ROS) which then attach the lysosomal membrane, causing lipid peroxidation and membrane loss (Pourahmada, 2003).

Similar to the kidney, nickel has also been found to cause stress in the ER of hepatocytes. Nickel acts by reducing ES-TRAP activity and indirectly inducing the expression of glucose regulating protein 78 (GRP 78). This ultimately leads to an imbalance in ER homeostasis (Hiramatsua, 2007).

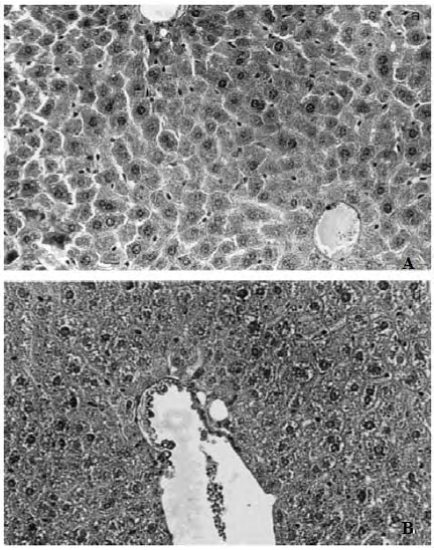


Figure 4-2: Histological sections of mice liver. Top: Normal liver of a control mouse given control injection of Hank's Balanced Salt Solution. Bottom: Liver section from a mouse after the fourth week of receiving 300 mg/kg BW/d nickel injection. Most notably: swollen hepatocytes are clearly seen in the parenchyma. (Pereira, 1997)

4.3.3.4 Blood toxicity

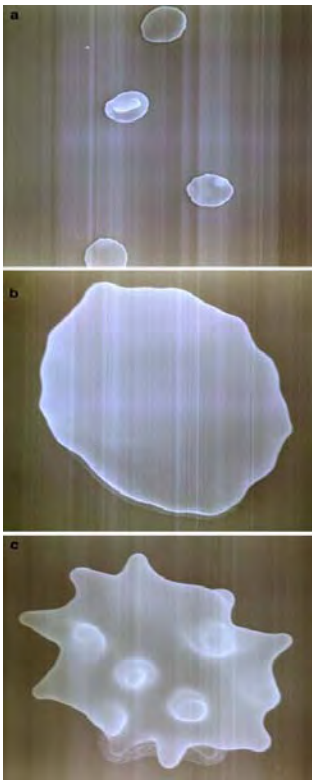


Figure 4-3: Effects of nickel chloride on the morphology of human erythrocytes. Scanning electron microscope image of: (a) untreated erythrocytes; (b) erythrocyte incubated with 0.5 mM $NiCl_2$, (c) erythrocyte incubated with 1 mM $NiCl_2$

Nickel induces multiple adverse effects on the blood. Exposure to nickel affects both the red and the white blood cells. Nickel free radicals have been detected circulating in the blood after nickel exposure (Wang *et al.*, 1993). As seen in Figure 4-3, nickel induces oxidative stress, affecting red blood cells by altering the membrane and cellular components. In an experiment done by De Luca *et al.* (2007) human and fish erythrocytes were incubated in 0.5 and 1 mM solutions of nickel chloride. To test the effects of nickel on red blood cell morphology, transport kinetics and cellular components the GSH concentration, K+ efflux concentration, and sulphate influx concentration were measured
De Luca *et al.*, 2007). It was found that nickel causes a decrease in the GSH concentration because of

(decreased sulphate uptake (De Luca *et al.*, 2007). It is thought that nickel causes an alteration of SH-groups, cross linking the transporter and inducing a conformational change (De Luca *et al.*, 2007). Consequently as the transporters are altered, sulphate is no longer able to enter the cells, and oxidative stress causes the observed decrease in GSH (De Luca *et al.*, 2007). GSH deficiency encourages hemoglobin to aggregate, and alterations in cell shape (De Luca *et al.*, 2007). Furthermore, nickel causes an increase in K+ efflux, which further exacerbates the observed changes in cell shape (De Luca, 2007). Both the increase in K+ efflux and decrease in GSH cause cell shrinkage (Figure 4-3 (c)) (De Luca *et al.*, 2007).

4.3.3.5 Spleen toxicity

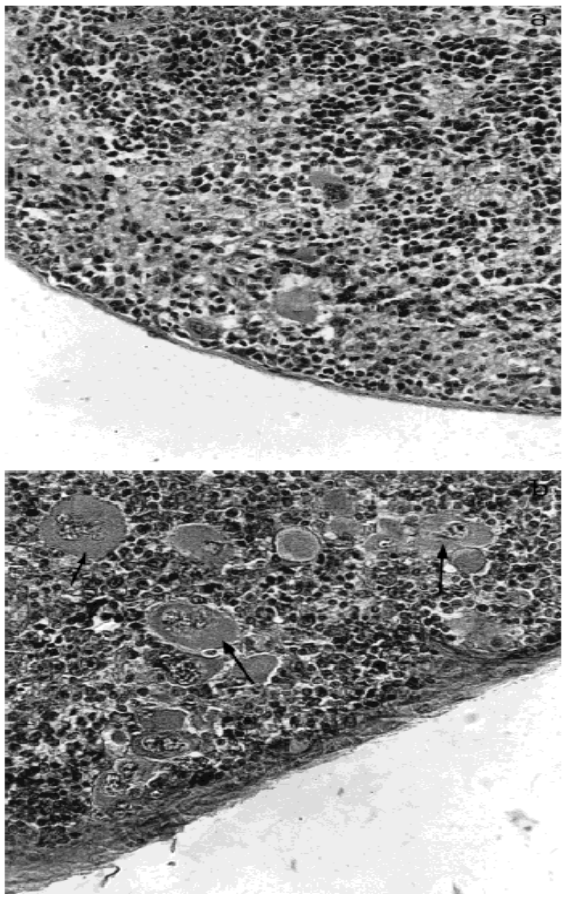


Figure 4-4: Top: A normal spleen in which clusters of lymphoid tissue are clearly visible through the organ; Bottom: splenic tissue from group from animal injected with nickel. Giant cells dominate the picture of the tissue.

Similar to the kidneys, the spleen accumulates nickel at an equal rate (Pereira *et al.*, 1997). In histological sections (Figure 4-4), the damage caused by nickel became apparent (Pereira *et al.*, 1997). Nickel exposure resulted in capsular fibrosis (Pereira, 1997). As well, there was an increase in the number and size of giant cells spreading throughout the entire organ. (Pereira *et al.*, 1997).

4.3.3.6 Dermal toxicity

Nickel induced allergic contact dermatitis is one of the most common reactions to nickel experienced by the general population. Allergic contact dermatitis is the result of a T-cell mediated immune response to haptens applied to the skin (Cavani *et al.*, 1998). Haptens are highly reactive molecules that couple with peptides and have the ability to induce an immune response (Cavani *et al.*, 1998). Sensitive people to a specific hapten such as nickel, will have rapid recruitment and expansion of hapten specific T-cells to the skin resulting in inflammation (Cavani *et al.*, 1998). Skin exposure to nickel in sensitive individuals induces both CD4+ and CD8+ T-cells, carrying an increased amount of interferon-ɣ, compared to normal individuals (Cavani *et al.*, 1998). Interferon-ɣ has antiviral, immunoregulatory, and anti-tumor properties (Cavani *et al.*, 1998). Secretion of interferon-ɣ from T-cells induces recruitment of lymphocytes to an area of inflammation (Cavani *et al.*, 1998).

Figure 4-5: Active eczema is evident on a nickel-exposed finger. The exposed finger (left) and the non-exposed finger (right) of the opposite hand of the same patient after 4 d of exposure to 100 mg/kg nickel (Nielsen *et al.*, 1999).

4.3.3.7 Pulmonary toxicity

Inhalation is a common route of exposure. Most of the population is exposed to nickel in the air at very low concentrations, however in certain cases of occupational exposure adverse effects are reported. Minor exposure could result in asthma, bronchitis, rhinitis, sinusitis, and pneumoconiosis. At higher levels, nickel has also been seen to cause a number of more serious and possibly lethal problems in the respiratory tract, including respiratory carcinomas as well as fibrosis of the upper airways.

In a study done by Zienolddiny *et al.,* (2000), nickel exposure resulted in increased incidence of lung carcinomas. It was found that nickel caused mutations in gene sequences (Zienolddiny *et al.,* 2000

Nickel inhibits the fibrinolytic cascade, which stops the breakdown of fibers (Andrew, 2000). This encourages the progression of fibrinogenesis in the lung which thickens the diffusion barrier and inhibits oxygen uptake, which ultimately leads to respiratory diseases such as asthma and bronchitis (Andrew and Barchowsky, 2000).

4.3.3.8 Brain

The inhalation of nickel has been found to affect the olfactory nerves and accumulate in the brain (Henriksson *et al.,* 1997). In most cases, it was found that nickel causes either hypoosmia or anosmia (increased or decreased ability to sense smell respectively) (Henriksson *et al.,* 1997). Besides accumulation in the brain, there were no lethal effects found from both inhalation and intraperitoneal injection of nickel (Henriksson *et al.,* 1997). It is suspected however that either an extremely large dose, or excessive exposure

might be detrimental, as nickel forms free radicals and causes lipid peroxidation (Henriksson *et al.,* 1997).

4.3.3.9 Testes

Exposure to nickel has negative effects on the testes. Animals exposed to nickel through injection were found to have decreased testicular weight, fertility rate. In addition, there was evidence of lipid peroxidation in the testes. However, the effects of nickel can be inhibited if treated with a chelating agent (Xiel *et al.,* 1995).

4.3.4 Human risk assessment

Nickel has been identified in at least 872 of the 1662 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ASTDR, 2005). The general population is exposed to low levels of nickel in ambient air, water, and food. Smoking increases nickel exposure, as does food consumption. It has been estimated that the average daily intake is 101-162 µg for adults. In males, daily intake ranges from 136ug to 140 µg. In females the range is thought to be between 107 µg/d to 109 µg/d . It has been shown that pregnant females average a daily dietary intake of 121 µg, and lactating females average 162 µg/d .

In the general population, about 5 µg of nickel a day is ingested through dietary supplements. Exposure though drinking water contributes another 8ug nickel per d assuming a total consumption of 2 L of water each day. Daily inhalation exposure is approximately 0.04ug. Communities surrounding nickel refineries typically experience the highest exposures (ASTDR, 2005). In Sudbury, an active nickel mining and refining site, daily exposure from water and air is thought to be 140 µg and 15 µg respectively. Leaching and corrosion of nickel from medical implements and preparations is another potential source of exposure. These sources include intravenous fluids, dialysis equipment, and prosthetics. Additionally, nickel-plated consumer goods and commodities such as steel coins and jewelry are other sources of exposure.

Occupational exposure to nickel is generally highest for those involved in the production and processing nickel. Major exposure routes for these individuals are dermal contact with nickel solutions, such as electroplating, nickel salts and nickel metal or alloys, and inhalation of aerosols, dusts, fumes, or mists containing nickel. A less significant exposure route involves ingestion of dust contaminated with nickel where poor ventilation exists (ASTDR, 2005).

4.3.4.1 Exposure in children

Children represent a special population with respect to nickel exposure since, children tend to drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. It is therefore important to appropriately characterize exposures in children.

Since children experience greater contact with floors and other surfaces, their exposures are expected to be higher where nickel-containing particulates have deposited (ASTDR, 2005). Concentrations of nickel in dust collected from homes in Ottawa, Ontario averaged 62.9 mg/kg with values as high as 116.4 mg/kg. Consumption of nickel through breast milk averages 0.8 µg/d between 4 and 38 d postpartum. For an average 3 month old child, the estimated daily intake of nickel through consumption of breast, bottled, dried and evaporated milk is below 2 µg/d . However, exposure is higher following consumption of some formulas and soy milk with estimates as high as 21 µg/d and 315 µg/d respectively.

4.3.4.2 Industrial risk assessment

Industrial air pollution in the Russian-Norwegian border area has caused much concern during the last decade. Investigations in Russia and other European countries have shown nickel exposure to be a problem in towns where nickel is mined. The refineries in northern Norway cause nickel pollution in the entire Sor-Varanger municipality. In order to investigate individual nickel exposure and possible health effects from the pollution, urine samples were collected from 3671 participants in the municipality. Mean and median nickel concentrations were 0.9 µg/L and 0.6 µg/L respectively. Individuals who lived in the rural areas closest to the refineries had lower nickel concentrations than individuals who lived in the urban areas. Independent risk factors for nickel concentrations in urine were (a) being an urban dweller and (b) living close to areas with high-density traffic. The authors concluded that nickel exposure attributable to air pollution from Russian refineries was of major importance for people who lived in Sor-Varanger (Environmental Health Report, 2002).

4.3.5 Treatments and remediation

The suggested treatment for low-level exposure to nickel requires removal from exposure to nickel. As mammals are exposed to very low levels of nickel on a regular basis, the normal elimination of nickel is through protein carriers in the blood (Bradberry, *et al*., 2008). Nickel is primarily excreted in the urine; consequently diuresis will increase the rate of elimination (Bradberry *et al.*, 2008). This can be accomplished through treatment with intravenous fluid until nickel levels in the blood and urine have returned to normal (Bradberry *et al.*, 2008). The half life for nickel when given intravenous fluids has been found to decrease by 55% (Bradberry, *et al*., 2008). If vomiting does not occur, gastric lavage should be avoided to limit esophageal irritation (Bradberry, *et al*., 2008). Higher exposure levels can cause irritation to the dermis, the respiratory tract, and the gastrointestinal tract (Bradberry, *et al*., 2008). The treatment for dermal irritation includes treatment with an oral or topical steroid. Respiratory tract irritation from nickel can be treated as asthma would be, and additional exposures should be avoided (Bradberry, *et al.*, 2008).

High exposure to nickel can be treated with a chelating agent (Bradberry, *et al.*, 2008). The effect of chelating agents on nickel distribution depends on the both the form the

nickel compound and the lipid solubility of the chelating agent (Bradberry, *et al.*, 2008). Diethyldithiocarbamate (DDC) and triethylenetetramine dihydrochloride (TETA) are lipophilic agents that can penetrate cell membranes and have the ability to reach nickel which has accumulated in fatty tissues such as the liver and brain (Bradberry *et al*., 2008). On the other hand, hydrophobic chelating agents, such as EDTA, can improve renal clearance and decrease cellular accumulation of nickel (Bradberry, *et al*., 2008).

4.4 ENVIRONMENTAL FATE

4.4.1 Air:

Atmospheric nickel from human activities is mainly in the form of particulate aerosols. These particles are generally 0.1-2 µm in diameter and are smaller than nickel from natural origin (2-10 µm) (Environment Canada, 1994). The processes governing the fate of nickel in the atmosphere are the same processes that govern the transport of these small particles, of which 15- 90% are soluble (Nieminen *et al.*, 2007; WKB, 2004). They are removed by wet and dry deposition in similar amounts. On average, nickel has a residence time of 5-8 d in the atmosphere.

The only significant gaseous nickel compound is nickel carbonyl, which degrades in air and has a half-life of less than one minute. Furthermore, this suspended particulate material does not absorb infrared radiation, and is not expected to contribute to global warming or depletion of stratospheric ozone (Eisler, 1998; Environment Canada, 1994) In Canada, nickel concentrations in ambient air show considerable variation. In a remote area in the Canadian Arctic, levels of 0.38–0.62 ng m^3 were recorded, whereas a value of 124 ng m^3 was measured near an operational nickel smelter in Canada (Nieminen *et al.*, 2007).

4.4.2 Soil

Nickel found in the soil can be greatly increased from atmospheric fallout near Ni-emitting industries. Nickel leached by rainwater from surface A horizons will accumulate in B horizons, resulting in levels of nickel in surface A horizons being lower than deeper C horizons (Environment Canada, 1994). Several forms of nickel can be found in the soil matrix, including inorganic crystalline minerals or precipitates, free ion or chelated metal complexes in soil solution, or various formulations with inorganic cationic surfaces. The majority of nickel in the soil is easily adsorbed to Fe and Mn oxides, which are predominantly found in surface B horizons. Locations near nickel smelters in Canada such as Sudbury, Ontario have most of the area's nickel present as NiS because of reducing conditions and sulfur in the soil (Eisler, 1998).

Soil chemistry strongly influences the bioavailability of nickel, which is most often defined as nickel's solubility in the soil. Ionic nickel is so insoluble or strongly adsorbed to soil oxides and organic matter that the element is not readily taken up by organisms under normal aerobic soil conditions (Everhart *et al.*, 2006). Nickel is most soluble below a pH of 6 (Eisler, 1998), but its bioavailability is strongly influenced by other soil

parameters as well, such as level of hydrous Fe and Mn oxides, humic and fulvic acids, and the amount of phosphate in the soil (Everhart *et al.*, 2006).

In Canada, some soils are naturally enriched in nickel because of ultramafic bedrock. Its residence time in soil is estimated to be 3500 years (Environment Canada, 1994). The mean concentration of total nickel in Canadian soils is 22 μg/g, with a range of 1 to 67 μg/g (OME, 2001). Industrial releases can greatly elevate nickel levels in soil. For example, in Ontario, the Port Colborne nickel refinery has not been operational since 1984, but the concentration of nickel in the soil was in excess of 8000 mg/kg at some sites sampled in 2001 (OME, 2002).

4.4.3 Water

Nickel enters aquatic ecosystems in dissolved and particulate forms after anthropogenic release of effluents, leachates, and atmospheric deposition (Environment Canada, 1994). Nickel in aquatic environments generally occurs as soluble salts adsorbed or associated with clay particles or organic matter (Muyssen *et al.*, 2004). Increased salinity, phosphorous loading, or water hardness usually lowers nickel's concentration in surface waters and lessens the quantity of nickel available for uptake by organisms. Considering both particulate and dissolved forms of nickel, its transport, fate and bioavailability are strongly affected by pH, oxidation-reduction potential, ionic strength, concentration of organic and inorganic ligands (especially humic and fulvic acids), and Fe and Mn oxides. No data were found on the potential for volatilization or photochemical reactions of nickel in natural waters (Environment Canada, 1994).

Natural background levels of nickel in water are relatively low: in open ocean water levels range from 0.2–0.7 μg/L, and the levels in freshwater systems are generally less than 2 μg/L (Nieminen *et al.*, 2007). Baby and Alice Lake provide examples of nickel concentrations in aquatic environments situated near mining operations. In 1995, the two lakes, located in Sudbury, Ontario had concentrations of soluble nickel of 200 and 1200 μg/L respectively (Woodfine and Havas, 1995).

4.5 ENVIRONMENTAL HEALTH ASSESSMENT

4.5.1 Toxicological data

4.5.1.1 Aquatic Organisms

Effects of nickel uptake in aquatic species are variable between different organisms and environmental conditions (Environment Canada, 1994). The essentiality of nickel to aquatic animals is not established (Muyssen *et al*., 2004). It can only be confirmed as an essential metal for plants and cyanobacteria due to the documented role of nickel in the urease and hydrogenase metabolic pathways. For these organisms, deficiency levels range from 10^{-12} M to 2×10^{-6} M. Available data on invertebrates suggest active regulation of nickel, which could imply nickel essentiality because there are no known examples of non-essential metals for these organisms (Muyssen *et al*., 2004).

In aquatic organisms, nickel toxicity varies significantly among taxa. For instance, chironomids and some other fungi, microorganisms, and invertebrates are relatively tolerant of nickel, while mollusks and crustaceans show greater sensitivity to nickel (Environment Canada, 1994). Lethal ionic nickel concentrations for sensitive species range from 11-113 µg/L (Eisler, 1998). According to the literature, the most sensitive freshwater organisms in short-term acute toxicity tests were the mussel (*Anodonta imbecilis*) and the snail (*Juga plicifera)*. The 96-h LC50 for these organisms was 190 µg/L (soft water) and 102 µg/L (very soft water), respectively (Keller and Zam, 1991; Nebeker *et al.*, 1986). These values are compared to the acute 96 h LC50s listed in Table 4-10 (USEPA 2008).

Table 4-10: Acute 96 h laboratory toxicity tests of both marine and freshwater species

Species	Common Name	96 h LC50 (mg/L)
Crustaceans		
Acartia clausi	Calanoid copepod	2.1
Americamysis bahia	Opossum shrimp	0.6
Eurytemora affinis	Calanoid copepod	9.7
Gammarus sp.	Scud, Amphipod	13
Fish		
Channa punctata	Snake-head catfish	0.000007
Heteropneustes fossilis	Indian catfish	0.000048
Oncorhynchus mykiss	Rainbow trout, Donaldson trout	0.073
Cyprinus carpio	common carp	2.4
Cyprinodon variegatus	Sheepshead minnow	5.4
Morone saxatilis	Striped bass	6.3
Lepomis gibbosus	Pumpkinseed	8
Anguilla rostrata	American eel	13
Morone americana	White perch	13.7
Menidia beryllina	Inland silverside	15.3
Fundulus diaphanus	Banded killifish	46.1
Liza vaigiensis	Square tail mullet	47.1
Priopidichthys sp.	Plain-head perchlet	52.4
Gambusia affinis affinis	Mosquitofish	180
Mystus vittatus	Striped catfish	255
Insects		
Chironomus sp.	Midge	8.6
Trichoptera	Caddisfly order	30.2
Zygoptera	Damselfly order	21.2
Mollusks		
Amnicola sp.	Spire snail	15.1

Species	Common Name	96 h LC50 (mg/L)
Worms		
Nais sp.	Oligochaete	14.1
Dugesia tigrina	Turbellarian, flatworm	16.8

LC - Lethal Concentration Reference: USEPA, 2008

Only acute toxicity values are shown in Table 4-10, but known acute to chronic ratios for freshwater and marine species range from 30-36 and 6-9 respectively, as shown in Table 4-11 (Hunt *et al.*, 2002).

Table 4-11: Acute to chronic (ACR) values for selected species

Species	ACR
Mysidopsis	3.3
Haliotis rufescens	5.51
Atherinops affinis	6.2
Daphnia magna	30
Pimephales promelas	36

Reference: Hunt *et al*., 2002

Sub-lethal effects of nickel to various aquatic organisms are well documented. In fish, some adverse effects include surfacing, rapid mouth and opercular movements, convulsions, and loss of equilibrium (Eisler, 1998). Also, destruction of the gill lamellae may cause blood and tissue hypoxia, leading to death (Ellgaard *et al*., 1995). For benthic invertebrates, reduced species diversity is possible. Both fish and invertebrates are susceptible to tissue damage, genotoxicity, and decreased growth (Environment Canada, 1994). In amphibians, available data concerning susceptibility to nickel show a negative correlation between populations of treefrogs and toads. Population abundance of adult treefrogs (*Hyla crucifer*) declined with increasing atmospheric deposition of nickel, while abundance of toad tadpoles (*Bufo americanus*) declined with increasing nickel concentrations in ponds (Glooschenko *et al.*, 1992).

Bioconcentration factors (BCFs) vary between taxa and environmental conditions. BCFs for aquatic macrophytes range from 6 in pristine waters to 690 at sites near a nickel smelter. BCFs for crustaceans fall within a range of 10-39; for mollusks, 2-191; and for fishes, 2-52 (Eisler, 1998). BCFs of up to 1,700 have been reported in marine plankton. Furthermore, brown algae have a value of 500, suggesting that some food chain biomagnification may occur (NAS, 1975).

4.5.1.2 Terrestrial organisms

Similar to aquatic organisms, nickel toxicity to terrestrial organisms is also highly variable between organisms and environmental conditions. Information on sub-lethal effects from nickel toxicity to terrestrial species was available for avian, microbial, and plant species as discussed below.

The literature on the toxicology of nickel to avian species is limited, but the studies to be discussed demonstrate nickel's toxicity and essentiality in chickens (*Gallinus*

domesticus), as well as an increased susceptibility at younger life stages in mallards (*Anas platyrhynchos*). In newly hatched chickens, reduced growth rates occurred when fed a three week diet of over 300 µg Ni/ g of feed, and mortality was first observed when fed diets of over 500 µg of Ni/ g of feed. Nevertheless, nickel deficiency was observed in this same species, and adverse effects occurred from being fed diets less than 50 µg/ g of feed (Ling and Leach, 1979). Chronic exposure to mallards showed increased susceptibility of ducklings. When ducklings were fed over 800 µg of Ni/g of feed, adverse effects occurred such as ataxia, tremors, and significant mortality, whereas adult mallards fed over 800 µg of Ni/g diet showed no evidence of systemic or reproductive toxicity (Outridge *et al.*, 1993).

Nickel toxicity to microorganisms can alter soil processes mediated by microbiota. For example, the nitrogen cycle can be disrupted by nickel stimulating nitrification and nitrogen mineralization, which results in a loss of soil nitrogen through leaching. This could lead to adverse ecological effects in boreal forests where nitrogen is an important limiting nutrient (Environment Canada, 1994).

Nickel is essential for plant growth and some plants are very tolerant of high levels of nickel. However, high concentrations such as those in serpentine soils can produce adverse effects (Seregurin *et al.*, 2006). Nickel exposure to plants is mostly through uptake by the roots. Aerial deposition on foliar surfaces is another possibility, but most often, the particulate nickel cannot pass through the cuticle and enter cells (Nieminen *et al.*, 2007). General signs of nickel toxicity are wilting, reduced growth of roots and shoots, poor branching, deformation of various plant parts, decreased dry matter production, leaf spotting, abnormal flower shape, mitotic root tip disturbance, germination inhibition, and chlorosis that can lead to foliar necrosis (Environment Canada, 1994).

The bioaccumulation or bioconcentration of nickel is moderate for mammals and birds. However, the potential for bioaccumulation appears to be highest for lower animals, mosses, and higher plants (Irwin, 1997). Data available for nickel toxicity to terrestrial species is listed in Table 4-12 (USEPA, 2008).

Table 4-12: Toxicity of nickel to terrestrial species*

Species	Common Name	Endpoint	Value	Duration (d)	Response Description	Source
Plants						
Betula papyrifera	Paper birch	EC25	6 mg/kg††	5-21	Reduction in radical growth	USEPA, 2008
Lonicera tatarica	Tatarian honeysuckle	EC25	6 mg/kg†	5-21	Reduction in radical growth	USEPA, 2008
Zea mays	Corn	EC25	9.03 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Picea glauca	White spruce	EC25	21 mg/kg††	5-21	Reduction in radicle growth	Kukier and Chaney, 2004

Table 4-12: Toxicity of nickel to terrestrial species*						
Species	**Common Name**	**Endpoint**	**Value**	**Duration (d)**	**Response Description**	**Source**
Pinus banksiana	Jack pine	EC25	29 mg/kg††	5-21	Reduction in radicle growth	Kukier and Chaney, 2004
Hordeum vulgare	Barley	EC25	30.4 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Glycine max	Soybean	EC25	32.6 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Pinus strobus	White pine	EC25	35 mg/kg††	5-21	Reduction in radicle growth	USEPA, 2008
Avena sativa	Oat	EC25	62.7 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Triticum aestivum	Wheat	EC25	67.1 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Lycopersicon esculentum	Tomato	EC25	68.2 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Raphanus sativus	Radish	EC25	76.9 mg/kg†	31	Reduction in biomass	Kukier and Chaney, 2004
Picea mariana	Black spruce	EC25	78 mg/kg††	5-21	Reduction in radicle growth	Kukier and Chaney, 2004
Raphanus sativus	Radish	EC25	82.5 mg/kg†	31	Reduction in biomass	Kukier and Chaney, 2004
Phaseolus vulgaris	Bean	EC25	86.8 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Beta vulgaris subsp. vulgaris	Redbeet	EC25	87.1 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Beta vulgaris subsp. Cicla	Swiss chard	EC25	87.8 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Pinus resinosa	Norway pine	EC25	95 mg/kg††	5-21	Reduction in radicle growth	Kukier and Chaney, 2004
Lolium perenne	Ryegrass	EC25	122.0 mg/kg†	42	Reduction in biomass	Kukier and Chaney, 2004
Invertebrates						
Lumbricus terrestris	Earthworm	NOEC	1200 mg/kg††	56	Reduction in growth of whole organism	USEPA, 2008
Lumbricus terrestris	Earthworm	NOEC	1200 mg/kg††	56	Mortality	USEPA, 2008

EC – Effective Concentration; NOEC – No Observed Effect Concentration;
†Concentration of Ni per kg dry weight of plant shoot cut about 0.5 cm above the soil surface at harvest
†† Concentration of Ni per kg of soil dry weight

4.5.2 Environmental risk assessment

Many environmental factors influence the impact of anthropogenic releases of nickel to the environment. Nickel has been found to be essential for certain species of plants and animals. Nevertheless, elevated nickel uptake by organisms in contaminated environments, such as areas near mining operations, can cause a significant ecological impact. For the most part, nickel released to the environment ends up in the soil or water. Soil and water high in nickel does not necessarily imply risk to the function and diversity of an ecosystem (Eisler, 1998). For example, total nickel in soil sampled in Port Colborne in 2001 was in excess of 8000 mg/kg. However, nickel injury to sensitive species of vegetation has rarely been observed in Port Colborne after aerial release of NiO ceased when the refinery shutdown in 1984 (OME, 2002). Rather, its uptake by organisms is largely dependent on the metal's solubility in the matrix, which is in turn governed by the local environmental conditions. As a result, a site specific approach to risk assessment is preferred, and is usually localized to the area near the industrial site. Proper management procedures can limit its availability for uptake and allow minimal impact of elevated total nickel concentrations near Ni smelters and mines (Menzies *et al.*, 2007; Wolkersdorfer, 2008).

4.5.3 Treatments and remediation

Remediation approaches for nickel follow the same general approach applied to most heavy metal contaminated soils. Unlike organic chemicals and plastics, metals cannot be degraded chemically or biologically (Dybowska *et al.*, 2006). Taking this into consideration, physical or chemical barriers are usually created to block nickel exposure pathways in the soil. Physical barriers may be used for practical or economical reasons since they can contain nickel within a specific site. For example, soil may be covered by pavement for land designated to be developed for apartment or retail use (Environment Canada, 1994; Mullgian *et al*., 2001).

Chemical barriers are also commonly used for nickel remediation (Environment Canada 1994). The uptake of nickel by organisms is commonly associated with its solubility in water. Since its solubility is strongly influenced by the level of pH in the soil or water, liming is commonly used to raise the pH and remove soluble nickel from the matrix (Menzies *et al.*, 2007; Woodfine and Havas, 1995). This may have repercussions since it also makes other nutrients less bioavailable to plants. As a result, fertilizers are added to the liming regime, depending on the plant type and amount of lime used. This procedure may be repeated periodically to maintain soil pH at a level that ensures nickel's immobility. Less common remediation approaches include phytoremediation and repeated deep cultivation to lower concentrations in the rooting zone of most plants (Environment Canada, 1994; Woodfine and Havas, 1995).

4.6 CONCLUSIONS

The nickel ion is very close in size to both the iron and magnesium ions, and this facilitates the replacement of iron and magnesium with nickel. This can occur naturally or under certain substrate induced conditions. Certain human ureases and pyruvate carboxylases have been shown to exchange their native ion with another ion under certain conditions (Sigel and Sigel 1994). Nickel ions have a positive divalent charge and can interact with various amino acids residues on proteins; this may alter ionic interactions within the protein leading to alterations in structure and function. Nickel interacts with many proteins both inside the cell and in the blood. Investigating these interactions is worthwhile in the search for mechanistic information regarding nickel toxicity.

Nickel toxicity is an increasing problem, as it is a potent reproductive and developmental toxin. In addition, nickel behaves as an immunotoxicant at high doses. Furthermore, nickel is a known carcinogen, and further investigation is required to fully understand the mechanism. There is no evidence to suggest that nickel behaves as either a genotoxin or neurotoxin.

Nickel accumulates in the kidney, liver, the lungs, and brain. As nickel exhibits a short half-life, and in healthy individuals does not pose a threat. However, individuals exposed to nickel, occupationally, have much higher levels of nickel in their bodies and are at increased risk of adverse effects. This risk assessment of nickel has shown that everyday exposure through air and water does not constitute a threat to the public. However, in certain work related exposures, levels may be high enough to increase risk of pulmonary cancers if no precautionary measures are used. Children do not seem to be a particularly sensitive population.

Nickel is essential to some plants and animals, and release is increased by anthropogenic emissions. This increases only local concentrations in the air, soil, and water. Nickel in the environment is not readily available for uptake by most organisms, is not likely to bioaccumulate to higher trophic levels, and therefore is not an immediate threat. Since pH strongly affects the ability of organisms to uptake nickel in the environment, it is beneficial to lime the soil, neutralizing the pH, thereby protecting terrestrial organisms and aquatic species from reduced growth and toxicity associated with this element.

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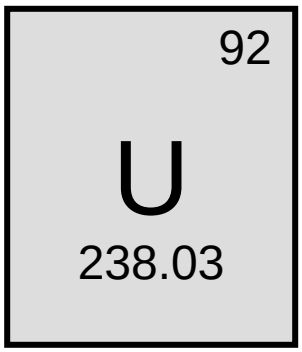
5 URANIUM



5.1 IDENTITY

Symbol: U

CAS No.: 7440-61-1

Electron configuration: [Rn] $5f^3 6d^1 7s^2$

5.2 CHARACTERISTICS

5.2.1 Physical and chemical properties

Table 5-1: Physical and chemical properties of uranium

Atomic number	92
Atomic mass	238.03 g/mol
Oxidation states	+2, +3, +4, +5, +6
Major Isotopes	^{238}U, ^{235}U, ^{234}U
Boiling point	4204 K
Melting point	1403 K
Ionization energies	1st: 584 kJ/mol 2nd: 1420 kJ/mol 3rd: 1420 kJ/mol
Electronegativity	1.38 (Pauling scale)
Density	19.05 g/cm
Physical description	Silver-grey metal, coated in black when exposed to air

Reference: Soloveichik (1993) as referenced by Craft *et al.* (2004) and ASTDR (1999)

After many steps of α and β radiation release, uranium can be transformed into lead. Over 19 isotopes of uranium have been identified (i.e. ^{222}U to ^{238}U). Natural uranium has been reported to contain three isotopes: ^{238}U, ^{235}U, ^{234}U, all of which are α emitters. Depleted uranium is mostly ^{238}U.

5.2.2 Sources

In 1841, it was found that the uranite discovered by Martin Heinrich Klaproth (said to have first discovered uranium) was not metallic uranium, but uranium dioxide (UO_2). Later, uranium tetrachloride (UO_4) was reduced to elemental uranium by heating in the presence of potassium. Metallic uranium has also been produced from sodium uranyl chloride.

Table 5-2: Natural sources of uranium

Uranite and Pitchblende	$UO_2 + UO_3$
Carnotite	$K_2O\ 2U_2O_3\ V_2O_3\ 3H_2O$ (uranium potassium vanadate)
Autunite	$Ca(UO_2)_2(PO_4)_2\ 10H_2O$
Torbernite	$Cu(UO_2)_2\ (PO_4)_2\ 10H_2O$
Coffinite	$U(SiO_4)_{1-x}(OH)_{4x}$ (uranium silicate)
Tyuyamunite	$Ca(UO_2)_2\ (VO_4)_2\ 5\text{-}8H_2O$ (uranium calcium vanadate)

Reference: from ASTDR (1999)

The uranium enrichment process involves the following steps: first, uranium dioxide (U_3OX) is produced from uranium ore, followed by fluoridation to produce UF_6. This UF_6 gas can be run through a separation column to obtain the three different isotopes of elemental uranium. Depleted uranium is chemically similar to both naturally occurring and enriched uranium. However, depleted uranium is about 40% less radioactive than either the natural or enriched forms.

Uranium is found in concentration of 2 - 4 mg/kg in the earths crust. Although there are over 100 different sources of uranium (i.e. uranium ore), the most abundant forms have been listed in Table 5-1. The largest uranium deposits are found in Canada and Australia. Canada is the worlds largest producer of uranium, producing approximately one-third of the world's total uranium. The world's largest uranium refinery is located in Blind River, Ontario, Canada. At this refinery, the concentrates of the uranium are refined largely to UO_3. At Port Hope refinery, also in Ontario, Canada, about 80% of UO_3 is converted to UF_6, which makes uranium ready for enrichment, and the rest is converted to UO_2.

5.3 MAMMALIAN HEALTH ASSESSMENT

5.3.1 Toxicokinetics/ toxicodynamics

5.3.1.1 Absorption, distribution, metabolism, excretion

Absorption of uranium through all routes of exposure (inhalation, oral and dermal) is low. Absorption of inhaled compounds takes place in the respiratory tract and depends on particle size. Absorption in the gastrointestinal tract can vary between 0.6 and 6% (ATSDR, 1999). Only particles less than 10 μm in diameter will reach the inner bronchioles and alveoli of the lung, and those that are successfully deposited in this area have a biological half life of 1 year (Craft *et al*., 2004). Uranium in body fluids is metabolized to the uranyl ion (UO_2^{2+}), the form with the greatest bioavailability, and is distributed systemically mainly in this form. This form can complex with citrates, bicarbonates or plasma proteins (ATSDR, 1999). Uranium has also been shown to deposit on calcium in bone surfaces, where it has a biological half-life of up to one year (Leach *et al*., 1973). The major route of elimination is excretion in the urine, with about 90% being eliminated within 24 h of intake. If the level of intake is sufficiently high (>70–100 μg/kg body weight), uranium can accumulate in the kidney and induce damage in the proximal renal tubules (Priest, 2001).

5.3.1.2 Cellular interactions

Uranyl ions form complexes with carboxyl groups and phosphoryl groups of biological molecules, but not with sulfhydryl groups. When bound with phosphoryl groups, uranium is associated with impaired sugar uptake by cells. Binding with phosphoryl groups is also associated with blockage of invertase activity, an enzyme involved with digestion (Rothstein, 1962). A proposed mechanism of action suggests that uranium is usually combined with bicarbonate or proteins while in the blood but in the kidney it is released from these transporters. While free in the kidney it is available to bind with phosphate and proteins in the tubule wall which leads to damage. These bonds are reversible and relatively weak, so uranium is released within a few d and excreted in the urine (ATSDR, 1999).

5.3.2 Toxicological data

5.3.2.1 Acute toxicity

Table 5-3: Acute toxicity data for uranium exposure in mammals

Route of Exposure	Species	Form	Response	Effect Measure	Reference
Inhalation (10min)	Rat	UO_2	LD10	630 mg/m^3	Leach *et al.*, 1973
Inhalation	Guinea Pig	UO_2	LD13, 30 d post exposure	637 mg/m^3	ATSDR, 1999
Oral	Rat	Uranyl Acetate	LD50	204 (100-416) mg/kg	Domingo *et al.*, 1987
Oral	Mouse	Uranyl Acetate	LD50	242 (155-327) mg/kg	Domingo *et al.*, 1987
Intravenous	Mouse	$UO_2(NO_3)_2$	LD50	10 - 20 mg/kg	CEPA, 1991
Intravenous	Rabbit	$UO_2(NO_3)_2$	LD50	0.1 mg/kg	CEPA, 1991
Intravenous	Guinea Pig	$UO_2(NO_3)_2$	LD50	0.3 mg/kg	CEPA, 1991
Intravenous	Rat	$UO_2(NO_3)_2$	LD50	1.0 mg/kg	CEPA, 1991
Sub-Cutaneous	Rat	Uranyl Acetate	LD50	8.3 (4.1-16.8) mg/kg	Domingo *et al.*, 1987
Sub- Cutaneous	Mouse	Uranyl Acetate	LD50	20.4 (17.0-24.5) mg/kg	Domingo *et al.*, 1987

5.3.2.2 Chronic toxicity

Table 5-4: Chronic toxicity data for uranium exposure to mammals

Species	Form	Duration of exposure	Dose	Response	Reference
Rat (male)	Uranyl nitrate hexa-hydrate	48 weeks	Not reported	Degeneration of the testes and depletion of	Maynard *et al*, 1953

Species	Form	Duration of exposure	Dose	Response	Reference
				germ cells	
Rat (male)	Uranyl nitrate hexa-hydrate	16 weeks	0.07 mg/kg BW/d	Decreased testes weight, testicular lesions, necrosis of spermatocytes	Malenchenko *et al*, 1978
Rat (male)	DU pellets (muscle implant)	72 weeks	3 levels	Accumulation in testes suggesting possible physiological consequences	Pellmar *et al*, 1999
Rat (male)	$UO_2(NO_3)_2*H_2O$	92-100 weeks	2 mg U/m^3	1% mortality	ATSDR, 1999
Rat (male)	UO_2	104 weeks	308 mg/kg BW/d	LOAEL	Maynard and Hodge, 1949
Dog	UO_2	260 weeks	5 mg U/m^3	4.5% mortality	ATSDR, 1999
	$UO_2(NO_3)_2*6H_20$	52 weeks	95 mg/kg BW/d	NOAEL	Maynard and Hodge, 1949

5.3.3 Toxicity

5.3.3.1 Endocrine toxicity

Uranium has the potential to cause toxic insult to the endocrine system by acting as an estrogen agonist, in a similar manner to other heavy metals, including cadmium. Uranium induces estrogen receptor (ER) responsive effects, as research has shown that exposure of animals to both uranium and an ER antagonist, inhibited the estrogenic effects of uranium. In one particular study, mice were used as an animal model to investigate the sub-chronic estrogenic effects of uranium in drinking water. Mice dosed with 0.005 μM uranium (given as 0.5 μg/L uranyl nitrate) from 30 d prior mating through to gestation showed a significant decrease in fetal female follicles *in utero* compared to a control group. Depleted uranium at levels as low as 0.06 μM (the lowest concentration mice were exposed to in this study) resulted in a significant increase in uterine weight, greater uterine luminal epithelial cell height, accelerated vaginal opening, and persistent presence of cornified vaginal cells (Raymond-Whish *et al*., 2007). A retrospective study on Namibian uranium workers correlated a six-fold increase in urine uranium levels with a significant reduction in testosterone levels, although the mechanism behind this toxicity is not understood (Zaire *et al.*, 1997).

5.3.3.2 Reproductive and developmental toxicity

Reproductive toxicity is related to endocrine toxicity if the endpoint is measurement of follicles and follicular development. Evidence for the reproductive toxicity of uranium is under debate, and difficult to assess due to the lack of human epidemiological data. Animal models have shown that high acute levels of exposure may produce direct

gonadotoxicity on the testes of males, while sub-chronic, lower levels of exposure seemed to have no effect on the testes morphology and function, but decreases in reproductive success may occur. Uranium's toxicity is dependent on the route of exposure. Uranium, when given orally or subcutaneously, exerts the greatest developmental toxicity on mice (Craft *et al.,* 2004). As with most developmental toxicants, the period of exposure during gestation is also critical (Domingo, 2001). Specific sub-chronic exposure (30 d) of rats to implanted uranium pellets did not affect the male reproductive tract, when sperm motility, sperm concentration, or reproductive successes were measured (Arfsten *et al.,* 2005). While Linares *et al.,* (2005) did not find that rats exposed to uranyl acetate dehydrate in drinking water for three months had deficient testes function; a dose-independent significant decrease in female pregnancies was reported. This may be associated with decreased testosterone levels which have been observed in Namibian uranium workers (Zaire *et al.,* 1997). Acute exposures of mice to 0.05 mM/100g body weight for seven d resulted in signs of extreme degeneration and potential necrosis of the seminiferous tubules, and decreased gametogenic counts (Jadon and Mathur, 1983). Chinese hamster ovary cells decreased in viability in a concentration-dependent manner after exposure to uranyl nitrate (ASTDR, 1999).

Developmental toxicity has not been observed among the F1 offspring of exposed rats. A sub-chronic study by Arfsten *et al.,* (2006) determined that offspring of the exposed male rats did not have altered morphology, neurodevelopment, or immune function. While many experiments have used rats as the model species for testing reproductive and developmental toxicity, mice are much more sensitive test subjects. Potential developmental toxicity has been discovered in mouse embryos. Exposure to 26 μg/mL uranyl nitrate induced the delay of embryo development and the impairment of blastomere proliferation (Kundt, 2000). Compelling results from the (Bosque *et al.,* 1993) study shows that subcutaneous exposure of pregnant mice to uranyl acetate (0.5, 1, and 2 mg/kg/d) for nine d caused a significant decrease in maternal body weight, dose-independent embryotoxicity, and some evidence of fetal malformations. Uranium may potentially decrease reproductive sex by decreasing the libido.

Exposure to enriched uranium ($^{235}UO_2F_2$) caused dose-dependent spermatotoxicity by generating chromosomal aberrations in primary spermatocytes and DNA strand breakage in sperm (Hu and Zhu, 1990). Chronic exposure of rat pups to enriched uranium *in utero* may cause developmental delays, specifically delayed hyperactivity amongst offspring (Houpert *et al.,* 2007).

While epidemiological data suggests that depleted uranium may be a teratogen (Hindin *et al.,* 2005), the FETAX assay did not support this claim (Mitchell *et al.,* 2005). A retrospective study assessing the congenital malformations of offspring who may have been exposed to military depleted uranium also did not find an increased incidence (Sumanović-Glamuzina *et al.,* 2003).

5.3.3.3 Immunotoxicity

Evidence of the immunosuppressive effect of uranium is limited. *In vitro* experiments have shown that depleted uranium induced apoptosis of a mouse macrophage cell line at doses as low as 1 μM in the form of depleted uranyl nitrate chloride. It has been suggested that active uptake of uranium molecules by macophages may initiate the process (Kalinich *et al.*, 2002). Apoptosis of rat alveolar macrophages was also observed with exposure to uranium dioxide (60 μg/mL) and depleted uranium (50 μM) (Tasat and de Rey, 1987; Gazin *et al*., 2004). Due to the high turnover of macrophages *in vivo*, apoptosis of macrophages has not been linked to overt immune modulation. Some immunosuppressive effects have been observed in epidemiological studies. Citizens in the Persian Gulf exposed to uranium experienced a higher prevalence of chronic fatigue, rashes, eye and ear infections, hair and weight loss, and coughing, all of which are symptoms of immune suppression (Doucet, 1994).

5.3.3.4 Neurotoxicity

There is research interest in the potential neurotoxic effects of uranium, as uranium accumulates in the brain. Recent reports have provided some of the strongest evidence for the molecular mechanisms behind the neurotoxicity of uranium. Several human case studies are available, although the exposure levels were not well documented. Kathren and Moore (1986) clinically investigated three men who had been acutely exposed to high levels of uranium (40-50 mg) during a work accident. No neurological defects or alterations could be detected in these men 38 years later. A case study involving a man who had been chronically exposed to uranium bars through industry exposure did experience significant neurodegeneration, displayed as foot cramps, leg pain, increasing gait disorders and a tendency to fall backwards. Ataxia, nystagmus, and peripheral neuropathy were discovered upon a neurological exam (Goasguen *et al*., 1982). A significant negative association was found between the exposure of Gulf War veterans to depleted uranium from shrapnel wounds, and performance accuracy and performance efficiency (McDiarmid *et al*., 2000). Assessment of veterans in a 1998 study by Kane *et al.* revealed that veterans who contained lodged depleted uranium pellets consistently had inferior results on neurocognitive tests compared to a control population.

Rat models experienced significant neurotoxicity, and exhibited significantly decreased ambulatory activity, weight gain, forelimb grip strength and transiently impaired working memory after exposure to 1 mg/kg or uranium acetate (Barber *et al.*, 2007). When rats inhaled uranium dioxide transiently for four weeks, they experienced significantly poorer spatial working memory compared with control rats (Monleau *et al.*, 2005). Hippocampal sections from rats embedded with depleted uranium fragments were analyzed. Six months after exposure to depleted uranium, the CA1 area of the hippocampus produced significantly smaller population spikes compared to the control, and these spikes had decreased input/output curves (Pellmar *et al.*, 1999).

Uranium interacts with several neurotransmitters to interfere with signaling pathways. This is the suggested mechanism behind uranium's neurological toxicity. Exposure to

uranium dioxide *in vitro* caused a significant decrease in the release of glutamate in the hippocampus, similar to other divalent heavy metals (Vietti and Lasley 2004). Bussy *et al.,* (2006) determined that uranium interferes with proper acetylcholinesterase activity in the cerebellum after 6 months of exposure of rats to uranium nitrate (40 mg/L) in water. Acetylcholinesterase levels in the striatum, hippocampus and frontal cortex were not affected. Jiang *et al.,* (2007) used fluorescent reporter proteins to assess rat cortical neuron degeneration after exposure to uranyl acetate. Uranyl acetate did not produce cytotoxicity, or significant changes in cellular energy metabolism, thiol metabolite oxidation, or lipid peroxidation *in vitro*.

5.3.3.5 Genotoxicity

Acute *in vitro* exposure of proximal tubular rat cells to uranium produced a dose-response curve for both apoptosis and DNA double-stranded breaks. The DNA damage was reversible at low doses (200-400 μM), but induced apoptosis at higher concentrations (Thiébault *et al.,* 2007). The Ames *Salmonella* reversion bioassay revealed a significant ability of uranium to produce mutagenic bacteria. A dose and time-related increase in mutagenicity was observed in rats exposed to depleted uranium implants when compared to control animals (Miller *et al.,* 1998). Speculation behind the mechanism of the genotoxicity of uranyl nitrate is derived from its affinity to phosphate, and its potential to bind the phosphate groups of DNA. In an i*n vitro* study, uranyl acetate formed a 1: 1 complex with ascorbate and subsequently produced single-stranded DNA breaks (Yazzie *et al.,* 2003).

Several retrospective analyses of populations exposed to uranium through NATO air strikes, uranium-containing shrapnel, nuclear fuel or uranium released during mining concluded that the subjects had a significantly higher level of chromosomal aberrations compared to control populations (Ibrulj *et al.,* 2007, McDiarmid *et al.,* 2004, Prabhavathi *et al.,* 1995, Meszaros *et al.,* 2005, Zaire *et al.,* 1996). The genomic instability and delayed micronuclei formation cited by Miller *et al.,* (1998) and Knöbel *et al.,* (2006) may contribute to cellular carcinogenesis.

5.3.3.6 Carcinogenicity

There are many epidemiological studies and case reports investigating the association between cancer rates and exposure to uranium. A case study in Iraq revealed that, in areas with higher levels of military attack and therefore higher depleted uranium levels, cancer rates were approximately five times that of the surrounding region. Specific cancers identified with an increased prevalence included lung, bronchial tube, bladder, skin, stomach and breast cancers, as well as an overall increase in leukemia (Aitken, 1999). Uranium nitrilotriacetate, a stabilized salt of uranium, has the ability to transform normal colon cell lines into neoplastic cells. High levels of genomic aberrations were discovered in these cells using the comet assay and FISH (Knöbel *et al.,* 2006).

Inhalation of uranium, as is common amongst uranium workers, may lead to the development of pulmonary fibrosis and neoplasia. This may be an effect of radiodecay

damage to the sensitive alveoli (ATSDR, 1999). Lung tumors have been observed after exposure to enriched uranium, and have been attributed to alpha-decay radiation (Batchelor, 1980). Rare cases of lung cancer have been reported after chronic inhalation of uranium.

5.3.3.7 Nephrotoxicity

Nephrotoxicity is the hallmark effect of uranium. The nephrotoxicity of uranium has been studied extensively, and several mechanisms have been demonstrated. Renal damage can be assessed d after acute exposure to uranium. The classic symptoms that arise from less than 15 g of depleted uranium over 15 d include proteinuria, elevated levels of non-protein nitrogen, abnormal phenol sulfonphthalein excretion, and potentially increased urinary catalase activity and diuresis (ATSDR, 1999). The greatest renal damage from uranyl nitrate consistently occurs in the S2 and S3 segments of the proximal convoluted tubule. Morphologically, these segments become dilated and undergo metaplasia to a squamous cell phenotype (Haley *et al*., 1982). Necrotic cellular casts are often present in the urine due to the direct cytotoxic effects of uranium on the proximal convoluted tubule cells. While Zamora *et al.*, (1998) reported that the characteristic markers for glomerular injury were not present in the urine of affected populations, glomerular damage has been observed in some animal studies, resulting in extremely high levels of plasma insulin and creatinine (Stopps and Todd, 1982). A retrospective study involving a low-exposure population (<1 µg uranium/L in drinking water) and a high-exposure population (2 to 781 µg uranium/L in drinking water) revealed that uranium specifically targets the proximal convoluted tubule. Uranium exposure has been positively correlated with glucose in the urine and serum ALP and BMG (Zamora *et al*., 1998). The LOEL for chronic uranium-induced nephrotoxicity was determined to be 4 ng/kg body weight (Zamora *et al*., 1998).

Several mechanisms have been investigated regarding uranium nephrotoxicity. Chronic exposure to uranium in drinking water up-regulates over 200 genes in kidney samples, and the up-regulation of several of these suggests that oxidative stress may be a mechanism of toxicity (Taulan *et al*., 2004). Chronic uranium exposure encourages the deposition of iron oxide in proximal tubule cell inclusions (Donnadieu-Claraz *et al.*, 2007). According to results found in separate *in vitro* studies, the cytotoxic action of uranyl ions is dependent on the surrounding phosphate concentration (Muller *et al.*, 2006, Carrière *et al.*, 2004). This suggests that the cytotoxic form of uranyl ions is a phosphate complex, and that the sodium-dependent phosphate co-transporter system provides a mechanism for uranium to enter the proximal tubule cells.

5.3.3.8 Osteotoxicity

Intramuscular exposure to uranium, often observed as lodged fragments of uranium-containing shrapnel in soldiers, causes the highest accumulation of uranium in the bone, and therefore the greatest osteotoxicity (Pellmar *et al*., 1999). Osteotoxicity is more prevalent in males than in females with chronic uranium exposure through drinking water, manifested as higher levels of bone resorption and measured using the serum

markers CTx and osteocalcin (Kurttio *et al.,* 2005). Bone formation was significantly inhibited among rats dosed with uranyl nitrate after molar extraction. Woven bone (a disorganized structure with a high proportion of osteocytes) was produced at a much lower rate than controls, suggesting the effects of uranium are not only seen as altered bone resorption but potentially as osteoblast inhibition as well (Guglielmotti *et al*., 1985). It has been confirmed that rats experience decreased bone formation and increased bone resorption after treatment with uranium (Ubios *et al.,* 1991). Osteotoxicity may also be a secondary result from direct action on the kidney, which can cause a greater fractional excretion of phosphate and calcium (Kurttio *et al.,* 2005).

5.3.3.9 Pulmonary Toxicity

Several studies have indicated that inhaled uranium does not penetrate the lungs. Inhaled uranium particles are normally caught in the upper respiratory tract and rarely migrate to the alveoli (Craft *et al*., 2004). Epidemiological studies show that workers exposed to air containing up to 9000 – 10,000 $\mu g/m^3$ of natural uranium do not experience any adverse effects (Polednak *et al.,* 1982).

Experimental studies on rats found that acute high levels of uranium inhalation caused widespread nasal hemorrhages and congestion. Intermediate exposures resulted in lung lesions, minimal pulmonary hyaline fibrosis, and pulmonary fibrosis in rats (Cooper *et al.,* 1982). These inflammatory and fibrotic changes were also observed in Syrian golden hamsters (Cross *et al.,* 1981). Long-term chronic exposure to uranium produced some cases of lung neoplasia in dogs (Cross *et al.,* 1981). Rat lung epithelial cells exposed to uranium *in vitro* experienced a significant decrease in proliferation after 72 h due to GSH depletion (Periyakaruppan *et al*., 2007).

5.3.3.10 Other Clinical Effects

Uranium has been shown to significantly induce several mixed function oxidase enzymes, including CYP3A1, CYP3A2, and CYP2B1. CYP3A1 mRNA expression was increased up to 900% in the kidneys of rats (Souidi *et al.,* 2005). These results indicate that uranium may affect the metabolism of other xenobiotics or endogenous compounds, and potentially cause secondary toxicities.

There is no evidence for gastrointestinal toxicity, hepatotoxicity, or cardiovascular toxicity due to uranium exposure (ATSDR, 1999). Similarly, no data were found describing any potential dermal toxicity of uranium (ATSDR, 1999).

3.4.4 Human Risk Assessment

Uranium has both chemical and radiological activities and as a result both are considered during risk assessment. Uranium is assessed based on route of exposure and its activities. Chemical uranium is found in both soluble and insoluble forms and is evaluated based on these properties. The regulatory levels vary, depending on the route of exposure, whether the exposure is occupational, and chemical and radiological properties.

The tolerable daily intake (TDI), and the annual limit of intake (ALI) are based on a 70 kg body weight, and derived drinking water concentrations (DDWC) are based on average consumption of 500 L/year. Values were determined using a number of animal studies after a number of safety factors were taken into consideration.

Table 5-5: Regulations for human ingestion of uranium

TDI (µg/(kg*d))	ALI (mg)	DDWC (µg/L)	Reference
2	51.2	102	ATSDR, 1999
0.7	17.9	36	Jacob, 1997
0.6	15.3	31	WHO, 1998
0.2	5.1	10	Konietka, 2005

Health Canada's interim maximum acceptable concentration (IMAC) for uranium in drinking water is 20 µg/L. The World Health Organization's provisional guideline for uranium in drinking water is 15 µg/L.

For the general population, the daily intake of uranium from each source for adults is estimated to be: air, 0.001 µg; food, 2.0 µg; and water, 0.6 µg. Thus, the total daily intake is approximately 2.6 µg, or 0.037 µg/kg body weight for a 70 kg adult. The majority (77%) originates from food, and most of the remainder comes from drinking water. Oral exposure levels are more than 10 times lower than the TDI and, as a result, are not a major concern for the general population.

Uranium in the air contributes a very small fraction to daily exposure to uranium (Health Canada, 2001). The tolerable air concentrations values for human exposure by inhalation were determined based on a number of animal studies, and after a number of safety factors were taken into consideration.

Table 5-6: Regulations for uranium in the air

Properties, duration	Tolerable air concentration ($\mu g/m^3$)	Reference
Soluble, intermediate	0.4	ATSDR, 1999
Insoluble, intermediate	8	ATSDR, 1999
Soluble, chronic	0.3	ATSDR, 1999

Daily exposure to uranium in Canada from air is estimated to be 1.43×10^{-5} µg/kg body weight, and the tolerable air concentration (TAC) is 0.2 µg/kg body weight for a 70 kg individual. The exposure to uranium from air is approximately 10,000 times less then the TAC and is not a major concern for the general population.

Overall, the total cumulative exposure to uranium from all sources is below both the TAC and TDI, so it is not a concern for the general population.

5.3.5 Treatments and remediation

Tiron as a chelator seems to be the most effective agent for the prevention of acute uranium intoxication, based on animal studies (Ortega *et al*., 1989). There are no recommendations for decreasing the absorption after peak concentrations have been reached following acute exposure to uranium. However, as uranium can complex with bicarbonate ions, sodium bicarbonate may be used to prevent the uptake of uranium into the systemic circulation, thus preventing uptake by critical tissues (Cooper *et al*., 1982). However, use of bicarbonate as a chelator to reduce absorption is limited because it seems to be effective only immediately after uranium exposure, as determined by animal studies. (Domingo *et al*., 1992)

5.4 ENVIRONMENTAL FATE

5.4.1 Environmental cycling

5.4.1.1 Air

Uranium is able to enter the atmosphere through anthropogenic activities such as mining, milling, or refining. Currently there is very little information about the abiotic transformations and degradations of uranium in the air. Uranium hexafluoride is the only compound with known information about its pathways in air. It immediately degrades into uranyl fluoride and hydrofluoric acid upon contact with water. Uranyl fluoride absorbs moisture in from the air and then settles out of the air at a more rapid rate (US EPA, 1999). Background levels of uranium in air range from $2.5 \times 10^{-8} – 10^{-7}$ mg/m^3.

5.4.1.2 Soil

Uranium in soil exists predominantly in 2 forms: insoluble U^{4+} and soluble U^{6+} (Bednar *et al*., 2007). The insoluble form, U^{4+}, can form ligands and complexes with natural organic matter; however the solubility of U^{6+}, which is usually in the form of uranyl ion UO_2^{2+}, has greater mobility in the soil as it moves through natural waters (Bednar *et al*., 2007). Interaction between the uranyl ion and inorganic ligands also plays a role in its mobility. For example, it has the ability to complex with carbonate (Elles and Lee, 1998). Background levels of uranium in soil range from 0.3 - 11.7 mg/kg (UNSCEAR, 1993).

5.4.1.3 Water

Under anoxic condition in water, uranium will be present mainly as the reduced form of U^{4+} (US EPA, 1999). This form is less soluble than the U^{6+} form present under the normal conditions of oxygen presence. The insoluble form of uranium (U^{4+}) usually forms salts and precipitates out of the water system, then integrating with sediment (US EPA, 1999). The U^{6+} form has the ability to form complexes with other compounds in the media such as carbonates. Bioavailable forms of uranium that can be found in water include UO_2^{2+} and UOH^+ (Charles *et al*., 2006). Background levels of uranium in ground

water range from 0.03 - 2.1 μg/L. In surface waters, the background uranium concentrations range from 0.003 – 2.0 μg/L (WHO, 2001).

5.5 ENVIRONMENTAL HEALTH ASSESSMENT

5.5.1 Toxicological data

5.5.1.1 Aquatic organisms

When aquatic organisms were exposed to uranium, there was a wide range of effects observed, ranging from lethality to reproductive problems and behaviour changes. The most sensitive species found in the literature was *Ceriodaphnia dubia* (Pickett *et al.,* 1993). They were exposed to uranium for 7 d, and reproduction was the measured endpoint. The EC20 value was found to be 0.003 μg/L. Chordata were found to have a high tolerance to uranium in the water. In two 96-h tests, the LC50 values were found to be 1570 μg/L (Markich and Camilleri, 1997) and 1965 μg/L (Riethmuller *et al.*, 2000). The full range of aquatic species that have been tested are summarized in Table 5-7. No data on bioaccumulation factors or acute to chronic ratios is available in the literature, although uranium is not expected to bioaccumulate.

Table 5-7: Toxicity of uranium to aquatic species*

Species	Duration of exposure	Concentration μg/L	Endpoint	Remarks	Sources
Chlorophyta					
Green algae (*Chlorella* sp.)	72 h	44	EC50		Franklin *et al*., 2000
Green algae (*Chlorella* sp. 12)	72 h	56	EC50		Charles *et al*., 2002
Cnidaria					
Hydra viridissima		0.2	EC40		Hyne *et al*., 1992
Green Hydra (*Hydra viridissima*)	96 h	108	EC50		Markich and Camilleri, 1997
Green Hydra (*Hydra viridissima*)	96 h	108	EC50		Riethmuller *et al*., 2000
Crustacea					
Ceriodaphnia dubia	7 d	0.003	EC25	reproduction	Pickett *et al*., 1993
Moinodaphnia macleayi	120 h	0.015	EC25		Hyne *et al*., 1992
Daphnia pulex	96 h	0.15	LC50		Trapp, 1986
Daphnia magna	96 h	0.9	EC25		Barata *et al*., 1999
Daphnia magna	48 h	5.9	EC50		Barata *et al*., 1998
Hyalella azteca	7 d	21	LC50	Soft Water	Borgmann *et al., 2005*
Daphnia magna	48 h	170	EC10	pH 7	Zeman *et al*., 2008
Daphnia magna	48 h	390	EC50	pH 7	Zeman *et al*., 2008
Hyalella azteca	7 d	1651	LC50	Hard Water	Borgmann *et al*., 2005

Species	Duration of exposure	Concentration µg/L	Endpoint	Remarks	Sources
Daphnia magna	48 h	7800	EC50	pH 8	Zeman *et al*., 2008
Magnoliophyta					
Duckweed (*Lemna aequinoctialis*)	96 h	758	EC50		Charles *et al*., 2006
Mollusca					
Velesunio angasi		0.01	EC20	behaviour	Brown and Markich, 2000
Velesunio angasi		0.01	EC20	behaviour	Markich *et al*., 2000
Mussel (*Velesunio angasi*)	48 h	634	EC50		Markich *et al*., 2000
Fish					
Brachydanio rerio	96 h	3	LC50		Labrot *et al*., 1999
Brachydanio rerio	96 h	3	LC50		Ribera *et al*., 1996
Catostomus lapinnis	96 h	44	LC50		Hamilton and Buhl, 1997
Purple-spotted gudgeon (*Mogurnda mogurnda*)	96 h	1570	LC50		Markich and Camilleri, 1997
Purple-spotted gudgeon (*Mogurnda mogurnda*)	96 h	1965	LC50		Riethmuller *et al*., 2000

*EC – Effective Concentration; LC – Lethal Concentration.

5.5.1.2 Terrestrial organisms

Toxicity of uranium to terrestrial organisms is summarized in Table 5-8. Uranium was reported to have been very toxic to some crop plants (Aery and Jain, 1998). *Triticum aestivum* had an EC25 of 0.5 mg U/kg, when looking for seed quantity. *T. aestivum* was also found to have an EC25 of 6 mg/kg, when looking at biomass yield (Gulati *et al.,* 1980). Other low values were also found in other crop plants, such as corn, sorghum, cotton and sugar beet which had an EC25 of 5 mg/kg for yield (Shevchenko *et al.,* 1987). Values for avian and bird species have not been reported in the data to date. There are no values for bioaccumulation factors in the literature, but due to the chemical properties uranium, it is not expected to bioaccumulate in the environment.

Terrestrial organisms have been shown to have low toxicity to uranium. The earthworms *Lumbricus* sp. and *Eisenia andrei* an EC25 and NOEC of 1000 mg U/kg respectively (Sheppard *et al.,* 1992; Sheppard and Evenden, 1992). Sheppard *et al.* (2004) has also demonstrated that the grass *Elymus lanceolantus* has a NOEC of 1000 mg/kg.

Table 5-8: Toxicity data of Uranium exposure to terrestrial organisms*

Species	Duration of exposure	Concentration (mg U/kg)	Endpoint	Notes	Reference
Collembolan					
Onychiurus folsomi		350	EC20	survival and reproduction	Sheppard *et al*., 2004

Species	Duration of exposure	Concentration (mg U/kg)	Endpoint	Notes	Reference
Onychiurus folsomi		92-190	EC20	survival and reproduction in find sand, pH 6.2	Sheppard *et al*., 2004
Folsomia candida		>710	EC20	survival and reproduction	Sheppard *et al*., 2004
Plants					
Triticum aestivum		0.5	EC25	seed number per spike	Aery and Jain, 1998
corn, sorghum, cotton and sugar beet		5	EC25	yield	Shevchenko *et al*., 1987
Tritican aestivum		6	EC25	biomass yield	Gulati *et al*., 1980
Arisida purpurea		50	LOEC	biomass increase	Meyer *et al*., 1998
Pinus sylvestris		>100	NOEC	growth	Sheppard *et al*., 1985
Elymus lanceolantus		1000	NOEC	emergence, length and biomass	Sheppard *et al*., 2004
Earthworm					
Eisenia fetida		1 μg/cm^2	EC25		Labrot *et al*., 1996
Eisenia fetida	96 h	13 μg/cm^2	LC50	contact test	Labrot *et al*., 1999
Eisenia fetida		40 μg/cm^2	LC50	contact test	Ribera *et al*., 1996
Lumbricus sp.	54 d	300	LOEC	survival	Sheppard and Evenden, 1992
Lumbricus sp.		1000	EC25	survival	Sheppard *et al*., 1992
Eisenia andrei	54 d	1000	NOEC	survival	Sheppard and Evenden, 1992

* EC – Effective concentration; LC – Lethal concentration; NOEC – No Observed Effect Concentration; LOEC – Lowest Observed Effect Concentration

5.5.2 Risk assessment

The risk of uranium contamination occurs mostly near uranium facilities such as mines and refineries. Some species terrestrial organisms of (Table 5-8) have EC25s less than the 11 mg/kg background concentrations that have been found near mines (UNSCEAR 1993). No information was found for birds.

Amongst aquatic organisms, *Ceriodaphnia dubia* is the most sensitive species, having an EC25 for reproductive effects at as low as 0.003 μg /L (Pickette *et al.* 1993). This falls into what the WHO (2001) has declared as background levels of 0.003 – 2 μg/L. Some tests have shown other species to have effective concentration values in this range (hydra

and some bivalves - Table 5-7). For the majority of species tested, the EC50 and LC50 values are much higher than the background concentration range.

5.5.3 Treatments and remediation

Areas contaminated with uranium have been treated and remediated in the past. Amending soil with phosphorus is a method to reduce the mobility of uranium (Seaman *et al*., 2001). Phosphorus in the soil is negatively charged and in the state of $H_2PO_4^-$ (under acidic soil conditions) or HPO_4^{2-} (under alkaline soil conditions) (Rufyikiri *et al*., 2006). The phosphorus reacts with the uranium in the soil to produce uranyl phosphates or other stable precipitate products (Rufyikiri *et al*., 2006).

5.6 CONCLUSIONS

Uranium is mined and enriched in order to make use of its radioactive properties. It is found in the environment in a number of forms with varying reactivities, mainly in soil and water. In water, background concentrations of uranium range from 0.003 to 2 µg/L. In soil, background concentrations of uranium range from 0.3 to 11.7 mg/kg. Uranium does not appear to bioaccumulate in the environment. Most aquatic and terrestrial species exposed to uranium in the environment do not experience adverse effects since EC50 and LC50 values for these organisms are generally higher than the levels of uranium present.

Human exposure to uranium occurs mainly through food and drinking water, although workers who mine uranium are exposed to higher amounts than the general population. Absorption of uranium is low through all routes. Uranium in the body is metabolized to UO_2^{2+} and can bind with calcium on bone surfaces or with plasma proteins. It is excreted mainly in the urine. With sufficiently high levels of intake, uranium can accumulate in the kidney and cause damage. In cases of acute exposure, Tiron can be used as a chelator, and there is some evidence that sodium bicarbonate may be effective in preventing uptake if administered soon enough.

There has been some evidence of various toxic effects, including reproductive, neurotoxic, nephrotoxic, carcinogenic, and genotoxic effects in mammals used in lab studies due to uranium exposure, however these have generally not been found in humans. Current exposures to the general population are more than 10 times lower than the TDI values, which range from 0.2 to 2 µg/kg/d , so exposure to uranium is not a significant risk to human health.

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